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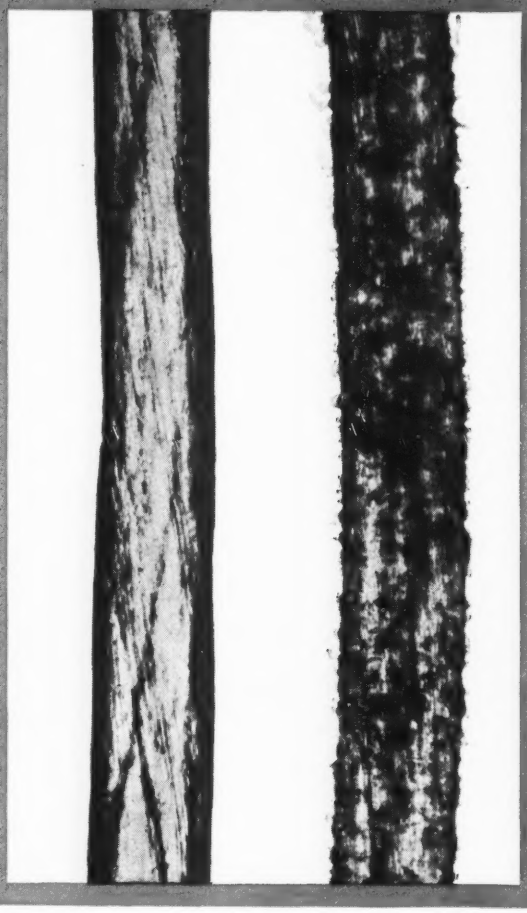
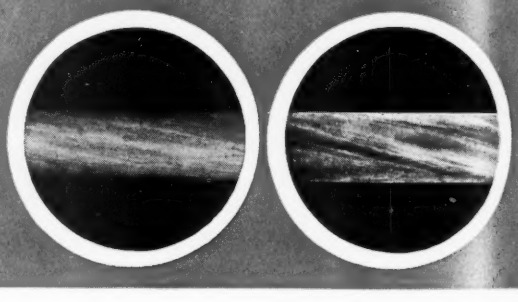


Photomicrography shows why D & G gut is stronger— more flexible



D & G gut

Photomicrograph* shows smooth surface of D & G SURGICAL GUT with no fraying or roughness. The soft matte finish prevents knots from slipping. No grinding to size. Full natural strength is preserved.

Another leading gut

Photomicrograph* detects surface fraying and roughness. This gut was ground to size. It appears uniform to the naked eye, but the powerful camera lens shows imperfections which may cause weakness when a knot is tied.

*Medium chromic gut, 5-0; light field method; 106 x

D & G gut

Photomicrograph** shows firm, even cohesion of plies—twisted into strands before chromicizing —for greater flexibility. Natural collagen firmly bonds the plies —holds the twist. This results in greater knot strength under stress.

Another leading gut

Photomicrograph** detects separate plies in this gut. Here each ply was chromicized before twisting into suture strand. This process limits natural bonding —lowers flexibility and tensile strength — encourages fraying.

**Medium chromic gut, 00; dark field method; 27 x

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THE EFFECT OF METHIONINE ON THE PRODUCTION OF MUCOPOLYSACCHARIDES AND COLLAGEN IN HEALING WOUNDS OF PROTEIN-DEPLETED ANIMALS

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RECENT STUDIES (3) have shown that a distinct pattern of normal wound healing can be described by data derived from estimations of the sequential formation of mucopolysaccharides and collagen in healing wounds. An inverse relation exists between the level of mucopolysaccharides in tissue and the amount of collagen present. The formation of the mucopolysaccharides precedes collagen formation reaching a peak around the third to sixth day and then falls rapidly as collagen is formed. On the basis of these studies we have suggested that wound healing be divided into two stages: (1) an initial productive phase in which the building blocks of repair are formed which lasts from the first to the fifth day after wounding, and (2) a collagen phase which begins on the fifth or sixth day and lasts until healing is complete. The present study is concerned with the effect of protein depletion on the production of mucopolysaccharides and collagen in the healing wound and the effect of methionine on these changes when it is added as a supplement to a nonprotein diet.

There have been several reports in the literature which indicate that methionine has a favorable effect on wound healing in protein-depleted animals. Localio was the first to show that the defective healing of wounds in rats fed a nonprotein diet could be restored essentially to normal by simply adding methionine to the diet. Williamson confirmed the effect of methionine on wound healing and also showed that a direct correlation existed between an increase in tensile strength and a retention of sulfur in the granulation tissue. Histologic investigations of the effect of methionine on wound healing were made by Perez-Tamayo and Ihnen.

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EXPERIMENTAL PROCEDURES

Eighty-two young albino rats weighing between 150 and 200 grams were divided

TABLE I

	Normal diet	No. est.	No protein diet	No. est.	Methionine supplement	No. est.
	HEXOSAMINE CONTENT OF HEALING WOUNDS (mgm./100 gm. dry tissue*)					
3 day wound	956	3	661	3	976	3
6 day wound	790	3	739	3	791	3
9 day wound	505	3	756	3	668	3
12 day wound	466	4	533	3	531	3
	COLLAGEN CONTENT OF HEALING WOUNDS (gm./100 gm. dry tissue†)					
3 day wound	8.8	3	5.2	3	7.0	3
6 day wound	9.9	3	9.6	3	10.5	3
9 day wound	22.3	3	16.0	3	18.7	5
12 day wound	31.1	4	17.1	3	27.4	7

*Normal skin, 450 mgm./100 gm.
†Normal skin, 71.9 gm./100 gm.

into three groups: (1) 26 animals receiving the normal rat purina chow diet and water ad lib., (2) 24 animals receiving the protein-free diet as described by Williamson, and (3) 32 animals receiving the protein-free diet supplemented with 0.147 per cent dl-methionine.

Wounding procedure. Five days after placing the rats on their respective diets, the animals were lightly anesthetized with ether. An area of skin between the scapulae was shaved and cleansed with isopropyl alcohol. Circles measuring 2.5 centimeters in diameter were outlined with India ink. A circle of tissue including the skin and superficial back muscle was excised within the outline. No dressing was applied to the wounds. At intervals of 3, 6, 9, and 12 days after wounding, the newly formed granulation tissue was excised, using the India ink mark as a guide to avoid inclusion of pre-existing connective tissues outside the wound area. Tissues from half of the animals were placed in acetone for collagen and hexosamine estimations. Tissues from the other half of the group were fixed in formalin and Zenker's solution for histologic studies.

Collagen estimation. The work of Abercrombie has shown the feasibility of quantitatively measuring hydroxyproline in samples of tissue from healing wounds. The specimens were dried, extracted in the autoclave, and hydrolyzed with hydrochloric acid following the method of Neuman and Logan. The hydroxyproline content of the hydrolyzate was determined by the modification of Martin and Axelrod. Collagen concentration, expressed as percentage of dry weight of tissue, was calculated by multiplying the hydroxyproline concentration by the factor 7.46 of Neuman and Logan.

Mucopolysaccharide estimation. The hexosamine content of samples of granulation tissue was determined by the method of Elson and Morgan as modified by Blix.

Histologic methods. Following fixation, the tissues were dehydrated, embedded in paraffin, and sectioned. Standard procedures were followed for staining with hematoxylin and eosin, Gömöri's reticulin stain, van Gieson's collagen stain, and Mallory's connective tissue stain. In addition, sections were subjected to the toluidine blue, periodic acid-Schiff, and colloidal iron techniques for the demonstration of mucopolysaccharides.

RESULTS

The results are shown in Figures 1 and 2 and Table I. The course of healing and the results of the chemical and histochemical studies in each group are presented.

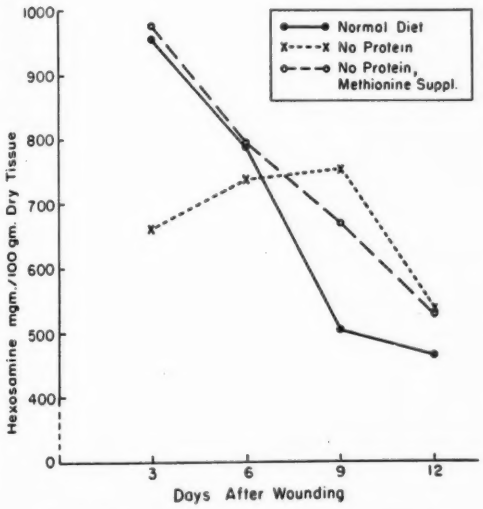

FIG. 1. Hexosamine content of healing wounds.

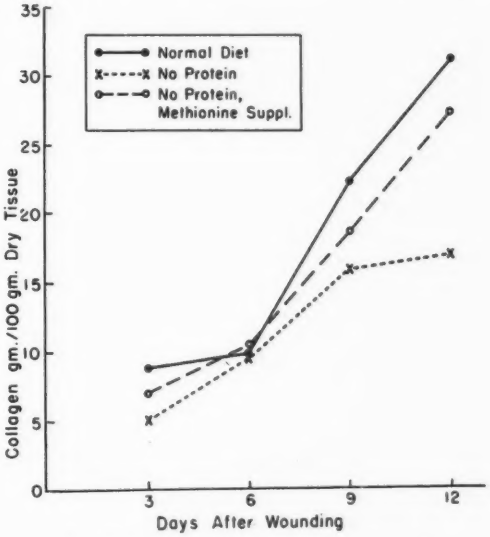

FIG. 2. Collagen content of healing wounds.

1. *Normal wounds.* The changes have been described previously (3) but are reproduced here for purposes of easy comparison.

3 Days.—Histologically there are large numbers of macrophages and fibroblasts in the wound. Capillary invasion of the granulation tissue has begun and the intercellular regions show a definite metachromatic reaction. Periodic acid-Schiff and Hale's stains are positive. There is a high level of mucopolysaccharides as estimated by glucosamine extractions (Fig. 1). No collagen can be demonstrated histoligically, but hydroxyproline assays indicate that 5 to 9 per cent of collagen is present in the wound (Fig. 2). This may be derived from the breakdown of tissues immediately adjacent to the wounded area.

6 Days.—The wounds are completely filled with granulation tissue. There are large numbers of normal-appearing capillaries and fibroblasts. The metachromatic properties of the ground substance are strong, as are the periodic acid-Schiff and colloidal iron reactions. The intensity of the colloidal iron stain is depicted in Figure 3a. There is already some evidence of a quantitative fall in mucopolysaccharide concentration as shown by the tissue levels of hexosamines (Table I) (Fig. 1). Now there are silver-staining fibers in the neighborhood of the fibroblasts and a few of these fibers have taken on the staining properties of collagen. This histologic evidence of collagen formation is confirmed by a clearcut and significant increase in hydroxyproline concentration (Fig. 2).

9 Days.—The wounds contain mature well oriented fibroblasts surrounded by abundant collagen fibers. The number of argyophilic reticulin fibers has diminished. During the 6 to 9 day period the collagen content has risen very rapidly, as shown by the hydroxyproline estimations. During this same period there has been a marked decrease in the amount of metachromatic and colloidal iron reactive material. The periodic acid-Schiff reaction has not decreased to quite the same extent. The hexosamine level is tending toward the pre-wounding levels.

12 Days.—The wounds now show a considerable decrease in the number of fibroblasts and those which remain are quite mature. The metachromatic properties of the ground substance are almost completely absent and the colloidal iron stain is nega-

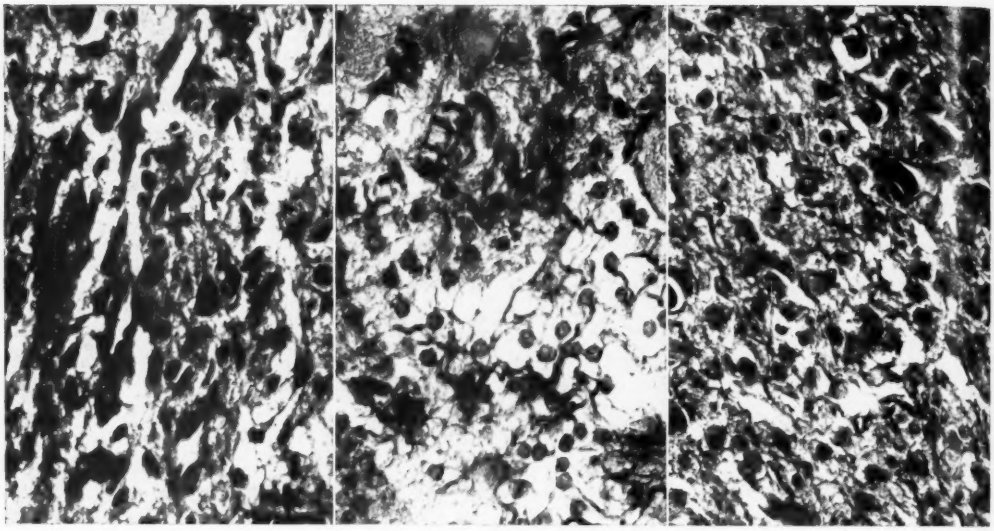

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FIG. 3. a, Photomicrograph showing a normal 6 day wound stained by Hale's colloidal iron technique. Note the heavy, dense staining which appears as a rich blue but is dark in the black and white print. This represents the peak of the intensity of the colloidal iron stain. ×350. b, Photomicrograph of a 6 day hypoproteinemic wound stained by Hale's technique. Note the marked reduction in staining material. ×350. c, Photomicrograph of a 6 day wound in a protein-depleted animal supplemented with methionine. Although the intensity of the stain is not normal, it is denser than that seen in b. ×350.

tive. One does see, however, a continued positive reaction to the periodic acid-Schiff stain. The hexosamine content of the tissue corresponds to that of normal skin. No reticulin fibers can be seen, and there are well defined, firm collagen fibers, as shown in Figure 4a. Similarly, the collagen content of tissue has reached a peak at which, from previous observations, we find it tends to level off (Fig. 2).

2. *Wounds in animals on a nonprotein diet*

3 Days.—The wounds show a lesser inflammatory reaction than normal. There are fewer macrophages as well as fewer fibroblasts present. The intensity of the metachromatic change, periodic acid-Schiff, and colloidal iron reactions are less than in normal wounds. This histologic impression is confirmed by the chemical extraction for hexosamine which is shown in Table I and Figure 1. There appears to be an impaired production of acid mucopolysaccharides in comparison with a normal wound.

6 Days.—The difference in the two wounds is not as striking histologically. On the protein-deficient diet one finds considerable granulation tissue. There are perhaps smaller numbers of fibroblasts and capillary formation is somewhat scanty. The fibroblasts, when studied carefully, appear pleomorphic and irregularly arranged. The metachromatic and periodic acid-Schiff reactions are less intense than those observed in the normal wound. Similarly, Hale's colloidal iron stain shows less evidence of mucopolysaccharides (Fig. 3b). There is a continued slow increase in the hexosamine level of the tissue. Silver stains show positive reactions but much less than in normal tissue, and no significant amount of collagen can be seen histologically. Chemical studies for collagen show no significant difference at this stage between the normal and the protein-depleted animals.

9 Days.—The wounds contain large numbers of immature fibroblasts with small

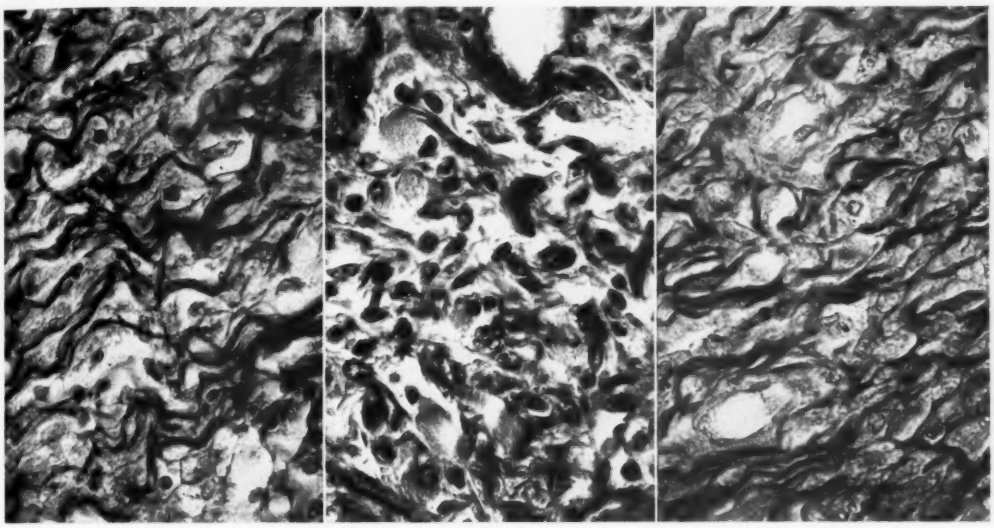

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FIG. 4. a, Photomicrograph of a normal 12 day wound. Note the rich network of interlacing, darkly staining collagen fibers. Van Gieson's stain, ×525. b, Photomicrograph of a 12 day wound in a protein-depleted animal. Note that there is little or no collagen. The wound is very cellular and the arrangement of the fibroblasts is irregular and disoriented. This resembles a normal 4 day wound. Van Gieson's stain, ×525. c, Photomicrograph of a 12 day wound in a protein-depleted animal on a methionine supplemented diet. Note the large number of collagen fibers and the fairly normal orientation. The wound is perhaps a little more cellular than normal, but the difference is not striking. Van Gieson's stain, ×525.

nuclei. Silver stains remain positive as do the colloidal iron and periodic acid-Schiff stain. It is evident that the wound is undergoing a change in the direction of normal but at a slower rate than the normal wound. In contrast, the curve of hexosamine concentration is of particular interest as it is still rising. It is now at its peak but well below the peak in normal wounds which occurs on the third day. At this stage in a normal wound, as previously noted, the concentration of acid mucopolysaccharides is diminishing as seen by both chemical and histochemical analysis.

12 Days.—The wounds have changed very little since the ninth day by histologic examination. There is now a fall in hexosamine concentration but no increase in collagen formation. The wounds are quite cellular and could easily be mistaken for a 3 day or 6 day wound. The collagen fibers in a 12 day wound in which the animal was given no protein are shown in Figure 4b.

3. *Wounds in protein-depleted animals supplemented with methionine*

3 Days.—There is a striking difference between the protein-depleted animals and those in which methionine has been supplemented. When methionine is included in the diet, the wounds at 3 days appear essentially normal histologically. Fibroblasts are present in normal numbers. There is perhaps a little less inflammatory reaction and the arrangement of the fibroblasts appears more irregular. There is a positive stain for acid mucopolysaccharides by all three staining reactions. It is of interest that chemically the hexosamine concentrations in 3 day wounds with a methionine supplement are actually in the high-normal range. Although reticulin and collagen stains fail to reveal the presence of any fibers in the new granulation tissue, the hydroxyproline assays indicate that 5 to 9 per cent of collagen was present in the wound area by 3 days. This result is

similar to that seen in both the normal and low protein animals and may represent tissue collagen from adjacent tissues.

6 Days.—The methionine supplemented wounds appear much like the normal. The collagen and hexosamine concentrations are quite similar in the two cases (Figs. 1 and 2). Hale's colloidal iron stain is positive (Fig. 3c).

9 Days.—The methionine supplemented wounds proceed to heal quite normally. There is the same rapid increase in collagen and fall in hexosamine levels as that absorbed in the normal wound. Histologically, there are abundant amounts of collagen and already some decrease in reticulin.

12 Days.—The wounds have approximated the same stage of recovery as the normal. Reticulin fibers are now absent and dense, mature collagen bundles are seen. These appear grossly different from normal collagen, but their actual amount seems to be, if anything, greater than in a normal wound (Fig. 4c). The hexosamine level of the tissue has fallen but not to as low a level as the normal wound. Similarly, hydroxyproline assays show that there is not as much collagen in the methionine supplemented group as in the normal animal but the difference is not great. It is of interest in this connection that Localio in his work noticed that at 12 days the tensile strength of the methionine supplemented animals was not quite as high as in the normal animals.

COMMENT

It has been demonstrated by several workers that methionine added to a protein-free diet restores the tensile strength of rat wounds to normal. The present experiments show that this effect may be explained in part by an influence of methionine on the formation of mucopolysaccharides and collagen. In animals maintained on a protein-free diet, there is a distinctly delayed production of these materials in the wound area during 12 days of healing. Adding methionine to the protein-free diet restores these mechanisms toward the normal.

One of the apparent effects of methionine is to stimulate the production of the building blocks of repair, presumably, as Localio has suggested, from the animal's own tissues. When protein is omitted from the diet, the formation of capillaries, proliferation of fibroblasts, and production of ground substance and collagen are all greatly retarded.

Several mechanisms might be postulated to explain the action of methionine in restoring healing toward the normal. It is known that a large portion of the sulfur amino acids utilized in the healing of wounds in rats maintained on a protein-free, methionine supplemented diet are derived from the breakdown and utilization of liver and muscle proteins. It has been shown by Forbes that methionine greatly increases the biologic value of dietary protein and increases the nitrogen balance and nitrogen gain of rats. It is possible that methionine exerts a similar influence in increasing the efficiency of metabolism of the proteins derived from body tissues such as liver and muscle, permitting a more extensive utilization of this material in the repair processes.

Methionine may also act directly on the proliferation of the fibroblasts. Morgan and Morton have shown that cultured chick fibroblasts require sulfur amino acids. A synthetic medium lacking sulfur amino acids supports growth for only 8 to 12 days, whereas a medium with added methionine and cystine supports growth for 35 days. The fibroblasts cannot convert methionine to cystine in vitro, but in the intact organism this conversion can occur. Therefore, methionine may hasten repair by stimulating the growth, proliferation, and functioning of the fibroblasts.

Methionine probably acts in yet another manner. The formation of collagen in normal wounds was preceded by the deposition of quantities of mucopolysaccharides. This accumulation of mucopolysaccharides was greatly retarded in rats maintained on a protein-free diet. A considerable amount of sulfate ion is taken up and incorporated into the mucopolysaccharides of normal healing

wounds. It is further known that depriving animals of sulfur amino acids results in alterations of the mucopolysaccharides of the connective tissues. Thus, methionine may play a role in providing sulfate ions for the formation of sulfated mucopolysaccharides. However, the increased excretion of sulfate ion in animals on a protein-free diet suggests that there may be a lack of mucopolysaccharides to which the sulfate might attach itself. Whatever the case may be, methionine apparently restores the sulfate metabolism toward the normal. Considerably more study of this aspect of the problem is needed.

It has been shown in these and earlier studies that there is an inverse relation between the level of hexosamine (and material staining like mucopolysaccharides) in the wound area and the amount of collagen present. The hexosamine content reaches a peak just before the period of rapid collagen synthesis. From the sixth to the ninth days after wounding the hexosamine level falls rapidly while there is a rapid formation of new collagen. These observations lend support to the concept that collagen formation depends to some extent on the presence of acid polysaccharides. Once the fibers are formed, presumably the mucopolysaccharide material is removed.

SUMMARY

1. If rats are maintained on a protein-free diet, wound healing is retarded. Two major factors in this impairment of wound repair appear to be the decreased accumulation of mucopolysaccharides and retarded collagen synthesis.

2. Methionine added to the protein-free diet restores the accumulation of mucopolysaccharides and the formation of new collagen fibers to levels which approximate the normal.

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HISTOCHEMICAL STUDIES ON OSTEOGENESIS AFTER TRANSPLANTATION OF BONE

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STUDIES ON OSTEOGENESIS after transplantation of bone have largely considered the factors that affect well known histologic sequences of healing and tissue replacement. Reappraisals of these sequences of healing by histologic studies have been lacking. In 1948, McKelvie and Mann studied the role of alkaline phosphatase in osteogenesis using histochemical technique and postulated that the enzyme, alkaline phosphatase, was concerned more with the formation of the fibrocollagenous framework or matrix of the bone itself than with the impregnation of this framework with calcium salts. However, the formation of this fibrocollagenous framework or matrix is probably dependent on two factors: a protein component produced by the fibroblasts, which passes through several stages before becoming matrix; and a carbohydrate component—a complex polysaccharide—produced either by the mast cells or connective tissue cells, which results in a homogeneous matrix that is chemically and physically necessary for the ultimate deposition of adult matrix from the soluble nonfibrous protein produced by the connective tissue cells.

In this study, the presence and fate of the mucopolysaccharides in osteogenesis after transplantation of cortical bone have been observed by the periodic acid Schiff stain which depends upon the production of aldehydes by periodic acid from the carbohydrate moiety of the mucoproteins.

METHODS OF STUDY

This study was carried out on 48 dogs. Cortical grafts, measuring 6 to 10 centimeters, were transplanted into the radius of dogs. Sections were taken from the areas of regeneration at intervals of 1 to 170 days. All sections were studied microscopically in their decalcified state by hematoxylin and eosin stain, alkaline phosphatase stain, and the periodic acid Schiff stain.

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RESULTS

The periodic acid Schiff (PAS) stain adds a great deal of interest to the microscopic appearance of new bone formation and the information it provides in that: (1) a PAS positive reaction indicates the region first influenced by the stimulus to osteogenesis; (2) it identifies the mesenchymal cells destined to become osteoblasts; (3) it provides an indication of the osteogenic value of the periosteum and endosteum and their role in repair; (4) its presence around bone transplants indicates their osteogenic potential, and clearly differentiates between old and new bone.

In the animal, the inner cambium layers of the periosteum possess osteogenic properties; these cells stain PAS positive. The differentiation of fibroblasts to the osteogenic stage is seen by the changes in intensity of the stain from a light red to reddish purple. The fibrils thrown out by the osteoblasts can easily be seen and are undoubtedly associated with the formation of the fibrocollagenous material which is a precursor of adult bone.

In the region of the transplant, as the wound is healing, a hematoma is formed which stains PAS negative (Fig. 1). As Stirling has demonstrated, this reaction may be explained by the fact that a fracture hematoma shows a high acidity for the first 10 to 12 days indicating little or no

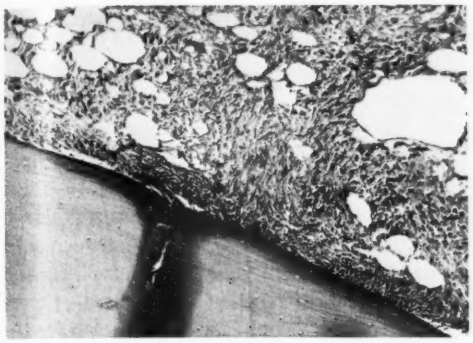

FIG. 1. Bone transplant 8 days after transplantation; a hematoma forms which is PAS negative.

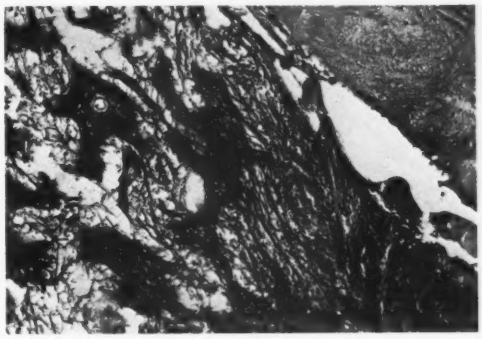

FIG. 2. Bone transplant 14 days after transplantation; callus forms which is PAS positive.

fibroblastic activity during this period. As the hematoma becomes organized the endosteal side of the host becomes PAS positive. From these regions osteoblasts and their precursors proliferate to form a firm callus which surrounds the transplants (Fig. 2). The endosteum and periosteum of the transplant stain PAS negative indicating no osteogenic activity from these regions.

During the first 10 to 14 days the haversian systems undergo a marked dilatation and necrosis and stain PAS negative (Fig. 3). As the haversian systems become filled with cellular elements, they become PAS positive (Fig. 4). In a few areas, especially those near the endosteal and periosteal surfaces, the cells stain PAS positive, a reaction indicative of visible cellular elements undergoing metaplasia into osteoblasts.

As "creeping substitution" begins, there is a gradual replacement of the transplants by active osteoblasts which are associated with the formation of new bone. The function of these cells is to develop and form adult bone which usually stains PAS negative (Fig. 5).

DISCUSSION

The histologic appearance of osteogenesis after transplantation of bone can be divided into four phases: an initial lag phase which is represented by the formation of a hematoma about the transplant; a phase of fibroplasia brought about by the proliferation of osteoblasts and their tendency to form a firm callus; a phase of "creeping substitution" in which there is gradual replacement of the transplant by active osteoblasts;

FIG. 3. Bone transplant 10 days after transplantation; haversian systems undergo dilatation and stain PAS negative.

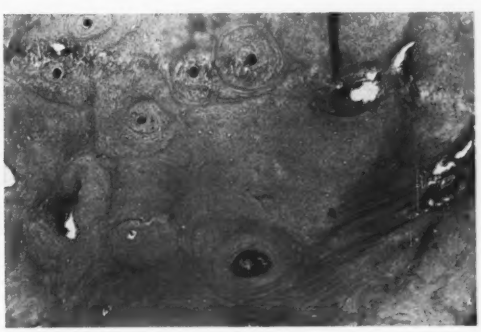

FIG. 4. Bone transplant 24 days after transplantation; the haversian systems become filled with cellular elements which stain PAS positive.

FIG. 5. Bone transplant 170 days after transplantation; total reconstitution in adult bone which stains PAS negative.

and the final phase of total reconstitution of the transplant.

The short phase during which the hematoma forms can be regarded as comparatively static, being largely concerned with the absorption of debris and dead cells in preparation for the fibroplastic phase and the invasion of the transplants with osteoblasts. This is supported by the fact that the hematoma shows an acid *p*H and the elements stain PAS negative which may be interpreted as not tending to form any matrix during this period.

After this initial phase, there is a rapid production of ground substance which is characterized by the transformation of the cellular elements into fibroblasts destined to be osteoblasts so that a firm callus surrounds the graft and fills the haversian systems. Although there is considerable controversy about the nature of the periodic acid Schiff stain, it is sufficiently specific for our purposes to indicate a carbohydrate fraction in the tissues. One may postulate that the fibroblasts secrete a soluble protein procollagenous substance that is essential to fiber and callus formation requiring a carbohydrate fraction in the ground substance. The mucopolysaccharides are probably secreted by the fibroblasts and mesenchymal cells which become osteoblasts.

During the phase of gradual replacement of the transplants by active osteoblasts, there is a pervasion of the transplant by a carbohydrate fraction of the ground substance. The fate of the osteoblast can be clearly demonstrated by the PAS stain. There appear to be more osteoblasts associated with the cellular extreme of the osteoid in a form other than osteocytes in the more mature states. Undoubtedly, some osteoblasts do persist as osteocytes but this fact does not account for them all. Osteoblasts can be identified which invade the transplant and persist in the osteoid in a form other than the osteocyte. These closely resemble the "matrix cells" identified by McKelvie and Mann which they believe constitute the noncalcific portion of the bone. These cells undergo disintegration liberating alkaline phosphatase, necessary for the impregnation of the transplants by calcium salts.

After the function of the osteoblasts has been fulfilled, adult type bone is formed. The only cells which contain osteogenic potential are the inner cambium layers of the periosteum and endosteum.

SUMMARY AND CONCLUSIONS

The osteogenesis after transplantation of bone has been studied by histochemical technique using the periodic acid Schiff stain which depends upon the production of aldehydes by periodic acid from the carbohydrate moiety of the mucoproteins.

The histologic appearance of osteogenesis can be divided into an initial lag phase, a phase of fibroplasia, a phase of "creeping substitution," and a final phase of total reconstitution.

From these studies, it can be postulated that a complex polysaccharide is necessary in order to produce a homogeneous matrix which is chemically and physically necessary for the ultimate deposition of adult matrix from the soluble nonfibrous protein produced by the connective tissue cells.

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NODE DISSECTION IN CANCER OF THE ENDOMETRIUM

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SINCE RIES, IN 1895, AND WERTHEIM, IN 1897, independently worked out the radical operation for cervical carcinoma, it has been taken for granted that such an operation should include excision of the pelvic lymph nodes.

This is not true of the surgical treatment of cancer of the endometrium. Until now it has been the general impression that such a dissection would be useless, for the notion has been widely held that carcinoma of the body metastasizes primarily to the aortic lymph nodes and that pelvic node involvement is rare and usually only a terminal phenomenon.

This is due to the fact that our knowledge of the lymphatic spread from the body of the uterus has been used mainly on autopsy studies.

PATHOLOGIC STUDIES

On the basis of his own investigations and a thorough study of the literature, Ewing reported that the lymphatics of the uterine body proceed, in 4 or 5 channels, through the broad ligament just below the tubes and then upward along the ovarian vessels. In the course of their passage through the parametrium and ovarian ligament, they communicate with the ovarian lymphatics to terminate in the aortic lymph nodes which are located in front of the aorta, from the bifurcation of the aorta to the diaphragm. From the lower part of the body of the uterus they anastomose with the cervical lymphatics. Thus, a cancer of the lower part of the body may metastasize to the same lymph nodes as a cervical carcinoma, i.e., to those in the obturator fossa, around the iliac artery and the iliac vein, as well as to the sacral lymph nodes.

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Novak's description of the lymphatics from the uterine body corresponds to Ewing's, but unlike the latter Novak maintains that low-seated cancer of the body may metastasize to the pelvic lymph nodes at a rather early stage.

Ewing states that metastases to these lymph nodes is a rather late phenomenon, pointing out that carcinoma of the body is characterized by spread through invasive growth, so that marked infiltration of the pelvic organs may occur without any involvement of the lymph nodes.

It should be mentioned that both authors agree that carcinoma localized to the fundus or the cornua has some tendency to involve the inguinal lymph nodes through the lymphatics in the round ligament, but that a metastasis by this route is a late phenomenon.

Henriksen made autopsy studies of the lymphatic spread in 420 cases of uterine cancer, 64 of which were carcinoma of the body. He found that, in principle, the lymphatic spread from the body was according to the pattern described.

It is striking that in Henriksen's series metastases to the pelvic nodes were just as common as to the aortic nodes. This indicates that pelvic node involvement is not so uncommon as has been assumed. Henriksen's studies also show that the two main groups (aortic and pelvic) can be involved separately, that uninvolvement of one group does not exclude involvement of the other, and—most important in this connection—that the pelvic nodes might be involved without involvement of the aortic nodes.

As Henriksen's investigations were performed on autopsy material, they do not afford information as to whether involvement of the pelvic nodes is as late a manifestation as maintained by Ewing or wheth-

FIG. 1. Age curves for the 45 patients operated upon for carcinoma of the endometrium compared with our first 100 patients who had a radical operation for cancer of the cervix.

er it may sometimes occur at an early stage as mentioned by Novak. This question can only be decided clinically, i.e., by systematic node dissection in the pelvis in the course of operations for carcinoma of the body.

As already mentioned, such a dissection was previously considered useless, as carcinoma of the body was believed to metastasize primarily to the extrapelvic lymph nodes (the aortics). In current textbooks and manuals by Te Linde, Meigs, and Martius, total hysterectomy with bilateral salpingo-oophorectomy is stated to be the procedure of choice in cancer of the body.

CLINICAL STUDIES

Recently there has been more interest in extending this operation to include the removal of the pelvic fatty tissue and the lymphatic tissue. Some of these studies will be discussed later. This extension of the procedure permits clinical investigation of the tendency of this carcinoma to involve the pelvic lymph nodes. Such studies are now possible because of the great advances of surgery. Today, we can perform these extended surgical interventions without essentially increasing the operative risk.

Javert has performed total hysterectomy, bilateral salpingo-oophorectomy, and dissection of the pelvic lymph nodes in 50 cases. In 14, or 28 per cent, he found involvement of the pelvic lymph nodes. This percentage is surprisingly high, particularly considering that systematic dissection was carried out in only 4 cases, whereas in the remaining 46 cases dissection was selective, i.e., removal of only a few enlarged lymph nodes. Therefore, his finding represents a minimum figure. The fact is that it is impossible to decide from its gross appearance whether or not metastasis is present in a lymph node. Frequently, greatly enlarged lymph nodes show only benign hyperplasia upon microscopic examination, whereas small, barely visible nodes may be the seat of definite extension as reported by Meyer and Howitz, Bonney, Henriksen, Brunschwig, Meigs, and others.

Javert's findings are of great theoretic interest. As they are supported by the observations of Randall and Ingersoll, we decided in 1953 to perform systematic dissection of the pelvic lymph nodes in all patients with cancer of the corpus uteri. Following is our experience during the first 2 years.

AUTHOR'S SERIES

Our series consists of 45 patients[1] with cancer of the uterine body, ranging in age from 35 to 73 (Fig. 1). Forty-one patients had a primary operation, whereas 4 were operated upon for recurrences following combined radium and x-ray therapy. Forty-one patients had a total hysterectomy with bilateral salpingo-oophorectomy combined with systematic dissection of the fatty and lymphatic tissue along the great vessels and in the obturator fossae, whereas 4 patients

[1]Some of the patients were transferred from the Gynaecological Department of the Copenhagen City Hospital.

had the extended Wertheim operation. There was no primary mortality and no complications which can be ascribed to this extension of the surgical procedure. The postoperative course was as might be expected, considering the patients' ages and their conditions. Patients with carcinoma of the body of the uterus have a tendency to obesity, cardiovascular disturbances, diabetes, and hypertension. Fourteen patients showed marked obesity and 3, hypertension. It is, therefore, not surprising that 4 cases of pulmonary infarct occurred. They were safely treated with anticoagulation therapy. In addition, pneumonia developed in 3 cases, and 1 patient had a persistent residual urine (following the Wertheim operation). The remaining 37 patients had no postoperative complications. They were discharged on an average of 12 days after the operation, except 1 patient who was given postoperative x-ray therapy.

The removed lymph nodes were cut into "step sections," i.e., from 50 to 250 sections were examined from each lymph node or group of lymph nodes.

SPREAD OF TUMOR AND FREQUENCY OF METASTASIZATION

In all 45 cases the diagnosis was made by preoperative curettage. Forty-two patients had typical uterine adenocarcinoma and 3 solid adenomatous carcinoma.

Examination of the uterus after removal showed no gross signs of tumor in 4 instances, indicating that all visible carcinomatous tissue had been removed in the course of the diagnostic curettage. In 10 cases the tumor was of the circumscribed papillomatous type, 11 showed well defined plaque-shaped carcinomatous ulcerations up to 3 centimeters in diameter, in the fundus, at the cornua, or on the anterior or posterior wall. The last 20 cases had diffuse or cauliflower-shaped, more or less necrotic masses occupying the entire uterine cavity or the greater part of it (Fig. 2). In 41 instances the tumor was limited to the uterine cavity, whereas in 4 it had spread as follows: in 1 case to the upper cervical canal, in 1 instance it had perforated the right fallopian tube, with an implantation on the right ovary and dissemination in the posterior cul-de-sac, and in 1 case there was destructive perforation of the corpus and bilateral ovarian metastases as large as hens' eggs. Lastly, there was in another case a metastasis 6 centimeters in diameter in the right ovary.

tumour	*invasive growth*			*x)* + *n*
	÷	+	+ +	
	3	1		2
	4	6		
		6	5	1
	1	7	12	4

x) + *n* - *positive node*

FIG. 2. This figure shows the extension of the tumor in the uterine cavity, the invasive growth in the myometrium, and the pelvic lymph node involvement among our 45 cases of cancer of the endometrium.

Figure 2 shows that invasive growth of the tumor in the myometrium was present in 37 cases. It was most common and most marked in the cases of greatest spread. However, in 1 case of a diffuse adenocarcinoma involving the entire uterine mucosa there was no invasive growth. According to Novak, such cases are by no means rare and they do not infrequently metastasize by the lymphatic route. In other words, lymphatic spread may occur before local invasive growth. In general, however, it seems beyond doubt that lymphatic spread is most marked in cases in which invasive growth is most advanced. This observation has been confirmed by Ingersoll, Javert, and Brun-

schwig. In our own series, this also holds true of metastases to the pelvic lymph nodes. According to Figure 2 pelvic node involvement was found in 7 cases. In 5 the tumor was extensive, whereas in 2 uteri there were no macroscopic signs of tumor. These were, however, special cases—patients with recurrences following combined radium and x-ray therapy 1 year and 6 months respectively prior to operation—so that the original extent of the tumors was unknown. Microscopic examinations revealed myometrial invasion in one of them, and no myometrial invasion in the other.

CASE REPORTS

The 7 cases with lymph node metastases are briefly summarized:

CASE 1. A patient, aged 48 years, had a large necrotic tumor in the lower half of the uterine body extending down into the cervix. Microscopic examination revealed adenocarcinoma with massive invasion of the myometrium. In each obturator fossa were 3 lymph nodes, as large as hazelnuts, showing severe carcinomatous infiltration.

The patient is alive with recurrence after a period of 2½ years.

CASE 2. A patient, aged 55 years, had an ulcerative tumor, 2½ by 3 centimeters in the left uterine horn. Microscopic examination revealed adenocarcinoma with moderate invasion of the myometrium. In the left obturator fossa was a lymph node, the size of a hazelnut, with marked carcinomatous infiltration. There was microscopic evidence of metastasization to the left ovary.

The patient is alive without recurrence or symptoms after 2 years.

CASE 3. A patient, aged 58 years, had a large, necrotic tumor occupying the entire posterior wall of the uterus. Microscopic examination revealed adenocarcinoma with very deep invasive growth. In both obturator fossae were lymph nodes as large as the kernels of hazelnuts, with massive carcinomatous infiltration.

The patient is alive without recurrence or symptoms after 1½ years.

CASE 4. The patient, aged 66 years, had a recurrence following combined radium and x-ray therapy 6 months before admission. A large, necrotic tumor occupying the entire corpus and perforating the uterine wall was present. Extensive metastases were found in both ovaries. In each obturator fossa were 3 lymph nodes as large as the kernels of hazelnuts, with severe carcinomatous infiltration.

The patient died with recurrence 8 months later.

CASE 5. The patient, aged 67 years, had a recurrence following combined radium and x-ray therapy 1 year before admission. There was no gross evidence of a tumor. Microscopic examination revealed myometrial invasion of an adenocarcinoma. Two pea-sized lymph nodes with carcinomatous infiltration were present in the left obturator fossa.

The patient is alive without recurrence or symptoms after 11 months.

CASE 6. A patient, aged 62 years, had a large tumor occupying the entire uterine cavity. Microscopic examination revealed adenocarcinoma with deep invasive growth. In both obturator fossae lymph nodes with massive carcinomatous infiltration were found.

The patient is alive without recurrence or symptoms after 6 months.

CASE 7. The patient, aged 60 years, had a recurrence after radium and x-ray therapy 6 months before admission. There was no gross evidence of a tumor. Microscopic examination revealed no invasion of the myometrium, but adenocarcinomatous metastasis to the left tube and to the lymph nodes in the left obturator fossa.

The patient is alive without recurrence or symptoms after 3 months.

Thus there was involvement of the pelvic lymph nodes in 16 per cent of the patients in our series.

Of the 7 cases, 1 (Case 4) must be called far advanced, and in such cases pelvic node involvement is not uncommon. The 6 other cases demonstrate that lymph nodes may be involved at an early stage.

The finding of a metastasis in the ovary as well as to the lymph nodes of the obturator fossa in 1 patient (Case 2) who had a well defined tumor in the left uterine horn exemplifies how in the early stages a metastasis may follow two routes: the lymphatic channels draining upward to the aortic nodes and those leading down to the pelvic lymph nodes. It shows, moreover, that a high situation of the tumor in the uterus does not exclude the possibility of a metastasis to the deep pelvic nodes. Incidentally, Ingersoll has reported a similar case.

Owing to the short follow-up periods, the present series does not afford information as to prognosis, not even regarding the prognostic significance of pelvic node involvement. Experience from the surgical treat-

ment of cervical carcinoma has shown, however, that lymph node involvement is of serious import. According to Javert, the same appears to apply to cancer of the corpus, and indeed this is not surprising. Javert reports that after a maximum follow-up period of 3½ years 76 per cent of the patients without pelvic node involvement were still alive, whereas only 28.5 per cent (4 out of 14) of the patients with such involvement were surviving.

Up to the present time, 41 of our patients are alive and symptom-free and without signs of recurrence, 1 is alive with recurrence, and 3 have died with large pelvic recurrences. The patient who is surviving with a recurrence (Case 1) had node involvement of both obturator fossae. One of the 3 patients who died (Case 4) had positive nodes, whereas the other 2 had no metastases to the pelvic lymph nodes, but 1 of them was the patient with extension to one adnexa and to the cul-de-sac. They all developed the recurrences 3 to 6 months after the operation. The 2 patients last-mentioned convincingly illustrate Ewing's contention regarding the tendency of carcinoma of the endometrium to spread by infiltration without involving the lymph nodes.

Our series is too small to permit far-reaching conclusions. In discussing the significance of metastases to the pelvic lymph nodes in corpus carcinoma, it is therefore reasonable to compare our results with similar investigations performed by other recent authors.

Table I lists some articles from the last 5 years. Among 217 patients with carcinoma of the endometrium operated on in various clinics, a total of 42 had involvement of the pelvic nodes which gives a rate of 19 per cent for metastases. There were no instances of primary mortality among these 217 cases. No doubt the difference in metastatic rate is explained by the relatively small size of each of the series. Comparing the results from the various series, however, it seems justifiable to conclude that together they show that carcinoma of the body metastasizes to the pelvic lymph nodes in nearly 20 per cent of cases.

TABLE I.—DATA ON 217 CASES OF CARCINOMA OF THE ENDOMETRIUM

Investigator	*Year*	*No. of cases*	+N*	*Per cent*
Randall	1950	20	4	20
Javert	1952	50	14	28
Ingersoll and Meigs	1952	25	3	12
Jordan	1954	20	4	20
Brunschwig and Murphy	1954	57	10	17
Present series	1955	45	7	16
Total		217	42	19

* +N=Positive nodes.

While so far it has been thought, mainly on the basis of autopsy material, that carcinoma of the body seldom metastasizes to the pelvic lymph nodes, and if so only in its terminal stages, the present investigations based on clinical, i.e., operative findings, show that such metastases are by no means uncommon and that node involvement may occur at an early stage.

DISCUSSION AND CONCLUSION

Of the 45 patients operated upon for cancer of the body of the uterus 7, or 16 per cent, showed involvement of the pelvic lymph nodes. Forty-one of these patients had a total hysterectomy with bilateral salpingo-oophorectomy and bilateral dissection of the pelvic lymph nodes, whereas 4 had the extended Wertheim operation as modified by Meigs.

Metastases occurred primarly in those cases in which the spread of the tumor had involved the juxtacervical part of the uterine cavity. In 6 cases of pelvic node involvement there was, moreover, invasion of the myometrium.

In 1 instance, however, a tumor of one uterine horn had metastasized to the lymph nodes of the obturator fossa. This patient also showed ovarian involvement on the same side. This case demonstrates that a carcinoma of the uterine body need not be of a juxtacervical situation to involve the pelvic lymph nodes and that the same tumor may metastasize by way of the lymphatics leading to the aortic nodes as well as those leading to the pelvic lymph nodes.

The fact that high-seated corpus carcinoma may metastasize to the deep pelvic lymph nodes is easily explained by the numerous anastomoses between the various lymphatic channels draining the various parts of the body. Our findings are confirmed by similar observations published by other authors during recent years. In these years, the interest in this problem has increased, probably as a consequence of the advances made in operative gynecology. The results from 5 clinics together with our own results show that lymph node metastases were present in 42 of the 217 patients with corpus carcinoma who had a dissection of the pelvic lymph nodes. In other words, the carcinoma of the endometrium involved the pelvic lymph nodes in 19 per cent. This rate is much higher than previously believed. In fact, it corresponds to the rate of metastasis to these nodes found in the radical operation for stage I carcinoma of the cervix (Meigs 19 per cent, Christensen and Lefèvre 24 per cent, and many others).

Thus the question arises as to the practical consequences of these observations. If carcinoma of the body involves the pelvic lymph nodes as often indicated by these investigations, it would at first sight seem appropriate to extend the traditional operative intervention to include also dissection of the fatty tissue, connective tissue, and lymphatic tissue of the pelvis, just as in the extended Wertheim procedure. This implies that cancer of the uterine body should be treated by an operation just as radical as that for cancer of the cervix. This attitude is taken by Ingersoll and Brunschwig who use the Wertheim operation or the extended Wertheim operation in all cases. However, their patients are selected. Brunschwig states, for instance, that his 57 cases constitute only about 25 per cent of the corpus cancers operated on since 1947. At the same time, however, he stresses that in the future he is going to use this type of surgical operation to a much greater extent. However right such an attitude may be theoretically, it must be borne in mind that decisive differences exist between the two forms of uterine cancer, that is, of the body and of the cervix.

In the first place carcinoma of the endometrium, unlike cervical carcinoma, metastasizes primarily into two main directions: to the lymph nodes above the pelvis and to those in the pelvis. Thus although the pelvic operation has been radical, there is no guarantee that all the carcinomatous tissue has been removed. It is possible, even likely, that several of the corpus cancers operated upon have metastasized to the aortic nodes. In the second place it must be kept in mind that patients with carcinoma of the uterine body are on the whole much poorer surgical risks than those patients with cervical carcinoma. Between these two groups there is a marked age difference as is apparent from Figure 1 which gives the age curves for the 45 patients operated upon for carcinoma of the endometrium compared with our first 100 patients who had a radical operation for cervical carcinoma. But there is another difference as well, one might say a constitutional difference, between these two groups of patients. Carcinoma of the body often affects women who are poor surgical risks, i.e., women with a tendency to obesity, cardiovascular diseases, hypertension, and diabetes, and this greatly increases the risk of using too radical an operation. A surgeon who operates for cervical carcinoma can select his patients. In operating for body carcinoma, he has to include a large number of patients of the category just mentioned. Therefore, any series of patients operated on for carcinoma of the corpus uteri is bound to include a large number who are poor surgical risks.

From the purely technical point of view, great difficulties are also connected with performing an intervention as radical as the extended Wertheim operation on many of these excessively fat patients. This is shown by Brunschwig's series in which uterovaginal fistulas developed in 6 patients, i.e., 11 per cent of the 57 patients operated upon. Consequently, the finding of the high rate of

metastasis to the pelvic lymph nodes in cancer of the body should lead to a more radical intervention only in suitable cases. In such instances, it seems reasonable to perform an extended Wertheim operation as it removes the lymph nodes and pelvic connective tissue as well as the upper portion of the vagina. This is a route by which corpus carcinoma metastasizes in no small number of cases.

In all other cases, it is no doubt wise to restrict the intervention to the classic operation. Whether it is to be extended to include also bilateral dissection of the pelvic nodes is a matter of discussion. In fact, little benefit can be expected from such lymph node dissection, when the pericolpic structures and a portion of the parametrial tissue with its lymphatics are left behind. In our series, however, there is one survivor (Case 2) without recurrence 24 months after an operation including removal of a hazelnut-sized lymph node with massive infiltration in the left obturator fossa. There is little doubt that this patient would long ago have developed a recurrence, if this lymph node and the attached lymphoid tissue had not been removed. Only time and experience can show whether our results can be improved by making the surgical treatment more radical. Removal of the lymph nodes may, moreover, afford important prognostic information and it can confirm or disprove the conclusions drawn by these preliminary investigations.

SUMMARY

1. Present knowledge concerning the lymphatic spread of carcinoma of the body of the uterus is primarily based on pathologic investigations, i.e., autopsy findings.

2. So far, metastasis from corpus carcinoma to the pelvic lymph nodes has been believed to be infrequent and to occur only as a terminal phenomenon.

3. This and other clinical investigations based upon dissection of the pelvic lymph nodes during operation for corpus cancer have shown that this form of cancer metastasizes to a greater extent and at an earlier stage to the pelvic lymph nodes than previously believed.

4. In 45 patients with corpus carcinoma 7 (16 per cent) showed involvement of the pelvic lymph nodes. When this series is combined with others reported by recent authors, a total of 42 out of 217 patients have had pelvic node involvement as reported by Randall, Javert, Ingersoll, Jordan, and Brunschwig. Accordingly, carcinoma of the body would appear to involve the pelvic lymph nodes in about 19 per cent of cases.

5. It would, therefore, seem logical to treat suitable cases of corpus carcinoma by the same operation as that used for cervical carcinoma, i.e., the extended Wertheim operation.

If the patient is not expected to tolerate so formidable an intervention, bilateral dissection of the lymph nodes in the obturator fossa and along the great vessels is recommended. Besides affording prognostic information, this procedure will confirm or disprove the conclusions drawn from the present, preliminary studies.

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HOARSENESS AND PAINFUL DEGLUTITION DUE TO MASSIVE CERVICAL EXOSTOSES

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SPURRING OF BODY MARGINS of the cervical vertebrae to an extent causing pain, radiation of pain, and limited neck motion is a well known entity. Infrequently, such a process of marginal proliferation becomes massive and the bulk of the new bone provides pressure to adjacent structures resulting in symptoms of hoarseness and difficulty in swallowing. Encroachment upon the esophagus and larynx is a mechanical change and is gradual while symptoms may appear rather suddenly. Four cases will be reviewed here.

The bronchologist may be the first to note such a disturbance when instrumentation of the esophagus becomes impossible because of a block. Deviation of the larynx may suggest a structural change in the cervical spine. Only a massive proliferation of bone will disturb passage of a bronchoscope whereas a smaller amount of new bone formation and its advance guard of soft tissue reaction will interfere with the use of an esophagoscope.

Clinically, the complaints of hoarseness and difficulty in swallowing may be outstanding. The esophagus is interfered with by direct encroachment of a large spur upon that structure with an early mechanical block. The spur is aided in producing the block by edema of the adjacent soft tissues, scar formation, or the presence of a tumor in the esophagus, as demonstrated in 1 case herein. Intolerance to solid foods is noted as the first indication of a narrow passage. Pain may accompany the act of swallowing. Long periods of difficulty in swallowing lead to degrees of emaciation if treatment is not instituted.

The onset of hoarseness is gradual and may be associated with a nonproductive cough. One patient complained of dyspnea and a sensation that the tongue was swollen. She complained that a speech defect followed the appearance of the tongue complaint.

Pain in the cervical spine area or radiation of pain from the neck region was not a major complaint in any of these patients. No history of pain of severe nature was brought out in the past history of any of these individuals. All patients complained of pain on swallowing, however. Motion of the cervical spine was limited in all cases. One patient demonstrated only minimal motion while the others had a fair degree of movement of the cervical spine.

Roentgenograms showed a variety of changes in the 4 patients. Multiple adjacent joint levels were involved in each instance with ankylosis of some of the segments. Extreme new bone formation in Cases 1, 2, and 3 was located at a level where motion was still present. Complete ankylosis tended to allow a smooth presenting surface to the proliferated bony prominence as in Case 4. The proliferation of a large amount of bone suggests a prolonged attempt at ankylosis. Motion of the involved joint or joints over a long period of time plays a part in producing large spurs since proliferation of bone would be expected to stop when complete bridging occurs.

Examination must include orthopedic, neurologic, endoscopic, and roentgenologic phases. Often a barium swallow will outline the esophagus and allow one to determine to some extent the amount of anterior soft tissue reaction. A firm bony mass may be palpated anteriorly in some cases. Endoscopy allows the determination and extent of extraesophageal obstruction, but may be of no value if the mass is too great, as demonstrated

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FIG. 1. Case 1. Barium shadow demonstrates anterior displacement of soft tissue structures over region of bone proliferation.

by Case 3. Neurologic evaluation is necessary to establish the clinical picture since the presence of neurologic disease may complicate treatment as in Case 2. Roentgenograms help establish the extent of the lesion. Lateral films of the cervical spine in flexion and extension may be helpful in demonstrating the degree of ankylosis at the various levels.

Treatment is difficult and must be planned for each case. In general, palliative therapy is not satisfying. Dietary changes due to difficulty in swallowing cause malnutrition. Gastrostomy is a method of by-passing the block and must be resorted to when poor nutrition is significant. The most positive approach is that of resection of the bony mass, but often other problems prevent this method, such as age, poor general health, and technical difficulties. Success of this procedure is entirely dependent upon the patient's ability to tolerate a major operation. In those individuals having coexisting medical problems in which surgery is contraindicated, a palliative course is dictated. Certainly a gastrostomy will delay or prevent many such patients from dying of starvation when the more radical procedures are forbidden.

CASE REPORTS

Four cases are presented which demonstrate some of the problems encountered in a small series. Fugazzola[1] reported on the problem of dysphagia due to the same causes in 1946.

CASE 1. C. R., a white male, aged 68 years, had a history of a gradual onset of hoarseness and pain in the throat on swallowing. The patient was reported to have recently recovered from a Bell's palsy. It was noted that a quite extensive osteoarthritis of the cervical, dorsal, and lumbar spines was present. The first five cervical vertebrae were fused as were the sixth and seventh segments. At the level between the fifth and sixth bodies, a definite proliferation of bone projected anteriorly and appeared to be the factor responsible for all the symptoms. No bronchologic examination or treatment was permitted because the patient was an inmate of a penal institution (Fig. 1).

CASE 2. A. K., a white female, aged 65 years, was first seen by Dr. Paul Holinger because of a complaint of dysphagia. Six months prior to admission the patient noted an acute onset of dyspnea with a sensation of having a swollen tongue. She noted difficulty in swallowing soon afterward. No peripheral nerve involvement was recorded at that time, and the patient was up and around in 2 or 3 days. She noted progression in her difficulty in swallowing and developed a speech defect. The progression of the dysphagia reduced her tolerance of foods from solids to liquids and upon admission, considerable difficulty was present when swallowing liquids. Upon examination, a poorly nourished individual presented with a speech impairment and a frequent cough. A gait disturbance was noted. Weakness of the left side of the face, inability to protrude the tongue, fibrillations of the tongue in addition to the dysphonia and dysarthria led to a neurologic diagnosis of pseudobulbar palsy probably on a vascular basis. Endoscopy revealed marked compression of the esophagus and larynx but this mechanical situation failed to account for all of the dysphagia present. There was moderate limitation of motion of the cervical spine. X-ray films revealed marked anterior osteoarthritic spurring at the level of third and fourth cervical vertebrae. Fluoroscopy and x-ray films using barium as a contrast medium confirmed embarrassment of the esophagus by the massive spur and an anterior displacement of the hypopharynx.

No attempt was made to remove the new bone formation in the presence of definite symptoms of intracranial vascular changes with palsy. The patient was discharged to be observed at frequent intervals until such time as a gastrostomy might be done, but the patient failed to return to the clinic (Figs. 2 and 3).

[1]FUGAZZOLA, F. Dysphagia due to cervical exostoses in osteoarthritis. Minerva med., Tor., 1946, June 16, pp. 507-508.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

FIGS. 2 and 3. Case 2. Large exostosis at level of the third and fourth cervical vertebrae pushes soft tissues forward as barium shadow shows in Figure 3. Ankylosis is incomplete at this level.

FIGS. 4, 5, and 6. Case 3. Massive proliferation before barium swallow in Figure 4, after barium study in Figure 5, and after resection in Figure 6. A carcinoma of the esophagus was found later at the level of the fourth cervical vertebra.

FIG. 7. Case 4. Note smooth contour of new bone growth when ankylosis is complete. Other cases demonstrated some motion and more irregular surface to exostoses.

CASE 3. P. H., a white male, aged 62 years, had a history of progressive weight loss, a frequent nonproductive cough, hoarseness, and pain in the neck region upon swallowing noted for about 6 months prior to admission. He could swallow no solid food at all upon admission. Emaciation was marked. Only minimal motion of the cervical spine was noted. X-ray films revealed obstruction of the hypopharynx and upper esophagus by large hypertrophic spurs of the cervical spine. A barium study showed a spill-over of food contents into the larynx and tracheobronchial tree. An aspiration atelectasis was also present. A Witzel gastrostomy was done under local anesthesia.

Following the gastrostomy, some weight was gained, but after 6 or 7 weeks, food backed into the esophagus from the stomach followed by frequent bouts of attempted vomiting. This condition caused pain in the region of the hypopharynx with repeated vomiting of mucus. Recumbency increased this local discomfort. The proliferation of bone was removed through an incision made parallel and just anterior to the right sternoclavicular muscle. The anterior longitudinal ligament was elevated after vital structures were retracted. Care was used to prevent sharp margins to remain at the points of resection.

The patient continued to have difficulty in swallowing following the surgery. Examination of the esophagus disclosed continued obstruction that would not permit entrance of a bougie. Several small pieces of tissue were removed from the area of stricture which revealed the presence of an epidermoid carcinoma. The patient was instructed to continue feedings via his gastrostomy and report periodically for observation. No record of a return to the clinics is present. The relation of the carcinoma to the long-standing external pressure might give rise to interesting speculation and will not be gone into here.

Because of the presence of the carcinoma of the esophagus, the resection of the bony mass had little chance to prove its value (Figs. 4, 5, and 6).

CASE 4. H., aged 71 years, was admitted to the hospital because of a fresh fracture of the right femur at which time a study of hoarseness and difficulty in swallowing was made. Both complaints were progressive and of 3 years' duration. Chiropractic manipulations at intervals during the last 2 years gave temporary relief for a throbbing headache and local neck pain. Bloody sputum was occasional. The patient was of large stature and quite obese making examination difficult. Local examination of the hypopharynx revealed bulging of the posterior wall without evidence of local inflammation above the prominence. An injected area was noted in the esophagus below the cricopharyngeus as seen with the esophagoscope. Slight paresis of the right vocal cord was seen. The trachea was deviated to the right. Motion of the cervical spine was restricted about 30 per cent in all directions and the anterior neck structure appeared prominent. No immediate therapy was instituted. A barium swallow outlined the mass noted in the lateral view of the cervical spine as noted in Figure 7. Ankylosis appeared complete between the third, fourth, and fifth cervical vertebrae.

SUMMARY AND CONCLUSIONS

Four cases are presented which demonstrate the extremes which may be noted in cervical exostoses due to osteoarthritic changes. In these cases older patients predominate. An occasional patient may derive definite benefit from wise surgery to remove the bony masses. All factors present will determine the course to be followed and the end result will depend upon the absence of coexisting pathologic conditions, such as carcinoma of the esophagus and central nervous system lesions.

Palliative surgery may prolong life and provide some comfort, as by gastrostomy.

INFILTRATING LOBULAR CARCINOMA OF THE FEMALE MAMMARY GLAND

HAROLD W. MILLER, JR., M.D., and SAUL KAY, M.D., Richmond, Virginia

EVER SINCE THE CLASSIC PAPER by Foote and Stewart in 1941 on lobular carcinoma of the breast there has been considerable controversy concerning the nature of this lesion. Admittedly, some of the earlier diagnoses may have been overzealous, but the basic principle upon which the diagnosis of such a condition rests still prevails. Undoubtedly, the personal equation exists in ultimately deciding whether a particular lesion is a florid type of adenosis, or actually represents lobular carcinoma in situ. Perhaps in large centers where considerable surgery of the mammary gland is done, it might be wise to follow patients with such questionable lesions closely. Most assuredly, considerable fortitude on the part of the surgeon and pathologist is necessary if such an attitude is adopted, and if careful follow-up studies are not practical, simple mastectomy might be the procedure of choice.

The purpose of the present report is to emphasize once again that lobular carcinoma can and does infiltrate the breast stroma, and that once infiltration occurs, the same dire consequences that follow ordinary scirrhous carcinoma of the breast can be expected. To the best of our knowledge only Godwin's article dealing with this problem can be found in the literature. In addition, the gross and microscopic features of lobular carcinoma of the breast are well described in Stewart's fascicle concerning tumors of the breast in the *Atlas of Tumor Pathology*.

REPORT OF CASES

CASE 1. E. D., a 47 year old white woman, was admitted to the hospital division of the Medical College of Virginia on the service of Dr. Carrington Williams on May 29, 1951, with a small mass in her left breast of 12 months' duration. The mass was asymptomatic. Physical examination revealed a firm mass in the upper outer quadrant with adherence to the skin. There was no lymphadenopathy. The right breast was normal. On the second hospital day a wedge resection of the breast lesion was performed. The pathologic diagnosis was sclerosing adenosis and the patient was discharged on June 2, 1951.

Her second hospital admission was on March 10, 1955 when she first noticed a "bruise" over her right breast with a slightly tender mass of 1 month's duration. Physical examination revealed an egg-sized mass in the lower outer quadrant, slightly tender to pressure and movable. There was no lymphadenopathy. On her second hospital day, from a biopsy and frozen section a report of fibrous mastitis was made. Permanent sections, however, revealed an infiltrating carcinoma of the lobular type. Three days later a right radical mastectomy was performed. She was discharged on March 30, 1955.

She was admitted for the third time on September 26, 1955 with a mass in the left side of her neck of 2 months' duration. This mass had gradually increased in size and was slightly tender. After her discharge she had received 7,500 roentgen units of radiation therapy to the right axillary region. Physical examination revealed a mass 3 by 5 centimeters beneath the left mandible which was very firm and tender. On September 28, 1955 a biopsy and frozen section revealed a metastatic tumor.

The pathologic specimen from the first operation in 1951 consisted of 3 pieces of left breast tissue, the largest 8 by 3 by 1 centimeter. All were similar, yellowish white, firm, and nodular. At microscopic examination, review of slides showed that the original diagnosis was in error. There were scattered small ducts solidly filled with uniform cells and rounded nuclei which sometimes showed prominent nucleoli (Fig. 1). A striking feature was the presence of individual similar tumor cells, loosely dispersed in the stroma. The diagnosis was carcinoma (lobular, infiltrating type) of the left female mammary gland.

The biopsy specimen taken in 1955 consisted of a segment of breast measuring 11 by 10 by 4 centimeters covered by a skin ellipse of 8 by 2 centimeters. Cut sections revealed firm, rubbery, white tissue. At microscopic examination small breast ductules sur-

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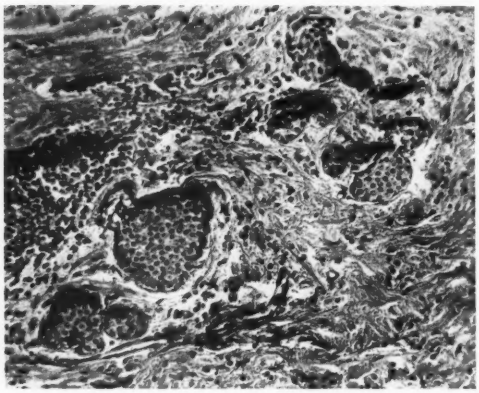

FIG. 1. Case 1. Left breast. Ductules solidly filled with tumor cells, some of which are scattered within the surrounding stroma.

rounded by whorls of neoplastic elements were a prominent feature (Fig. 2). The individual tumor cell dispersion within the stroma was similar to that noted in the left breast specimen removed in 1951.

The major specimen from the right radical mastectomy measured 34 by 17 by 5 centimeters and was covered on one surface by an ellipse of skin 20 by 10 centimeters in size. A previous biopsy incision 9 centimeters in length was present in the outer upper quadrant. The nipple was flat, and no definite mass was noted. The breast tissue was composed of a fibrous, nodular stroma and was extremely firm. It was especially hard in the upper half of the breast. The firm, apparently neoplastic tissue extended to within 5 millimeters of the pectoral muscle but did not appear to invade the muscle. Thirty-five lymph nodes were dissected from the axillary fat.

At microscopic examination tumor was noted in all quadrants save the lower inner quadrant. It was possible to show many instances of breast ductules surrounded by individual tumor cells which were often large and contained eosinophilic opaque material. Signet cell elements filled with mucicarminophilic material were also noted. All the lymph nodes removed showed evidence of metastatic tumor. The tumor cells within the lymph node were strikingly reminiscent of reticuloendothelial proliferation on superficial examination (Fig. 3). The diagnosis was carcinoma (lobular, infiltrating type) of right female mammary gland, with metastases to the axillary lymph nodes.

CASE 2. N. W., a 69 year old white woman, was admitted to the Sheltering Arms Hospital on the service of Dr. Robert Massie on January 11, 1954 with a mass in her left breast of 12 months' duration. There had been gradual enlargement and slight tenderness, but no nipple retraction or discharge. On physical examination, there was a firm, smooth mass, measuring 1 by 1.5 centimeters, in the upper outer quadrant of the left breast near the areola which caused dimpling of the skin. Several firm, palpable lymph nodes were present in the left axilla. On the fourth hospital day, a modified radical mastectomy, excluding the pectoral muscles, was performed. She was discharged on February 24, 1954.

Twelve months later she developed severe pain in her left hip and roentgenograms revealed metastatic tumor in the pelvis and lumbar vertebrae. Radiation therapy relieved her pain for a period of 6 months,

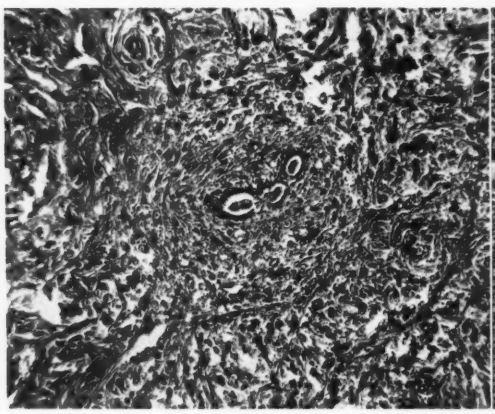

FIG. 2.

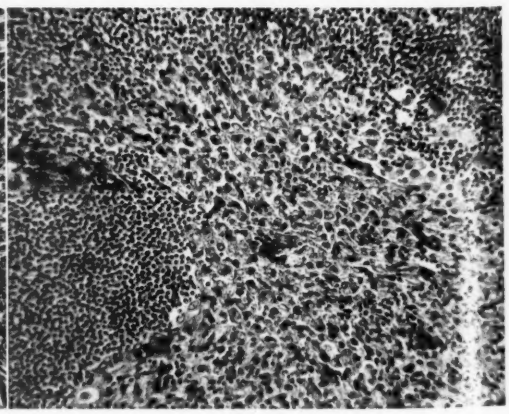

FIG. 3.

FIG. 2. Case 1. Right breast. Noncancerous breast ductules surrounded by whorls of neoplastic cells.

FIG. 3. Case 1. Metastatic right axillary node showing undifferentiated tumor cells resembling reticuloendothelial cells.

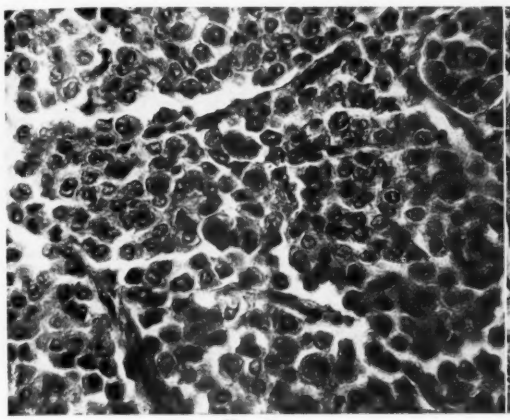

FIG. 4.

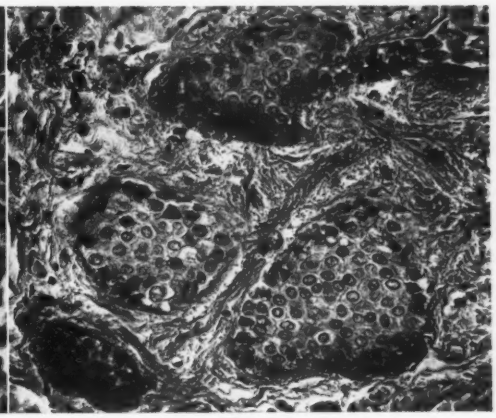

FIG. 5.

FIG. 4. Case 2. Undifferentiated epithelial cells in breast simulating reticulum cell sarcoma.
FIG. 5. Case 2. An area within the breast showing ductules solidly filled with tumor cells.

and she is now receiving testosterone for control of rather severe pain.

The pathologic specimen from the modified radical mastectomy (in that the pectoral muscles were not removed) measured 30 by 18 by 3 centimeters, and there was an ellipse of skin on one surface 17.5 by 17 centimeters in size. The nipple appeared to be fixed to the underlying structures. A mass measuring 2.2 by 2 by 3 centimeters was present in the upper outer quadrant. It was located 0.8 centimeter deep to the skin and 2.5 centimeters superior to the fascial plane. The tumor was light tan with small crevices on cut section. There was a smaller mass superior to the original tumor, 1.5 centimeters in diameter. Twenty-five lymph nodes were dissected from the axillary fat.

At microscopic examination the presence of tumor was noted in all quadrants except the lower inner. The main mass of tumor was composed of diffuse sheets of cells without organoid pattern. There was a striking resemblance to reticulum cells (Fig. 4). An area in the lower outer quadrant showed ductules and acini involved by similar neoplastic cells as well as individual tumor cells lying free within the stroma (Fig. 5). None of the lymph nodes dissected showed evidence of metastatic growth. The diagnosis was carcinoma (lobular, infiltrating type) of the left female mammary gland.

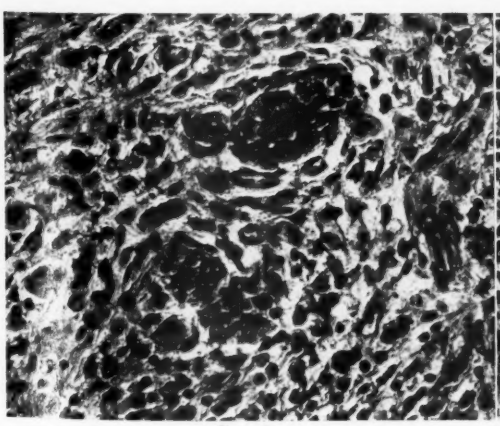

FIG. 6.

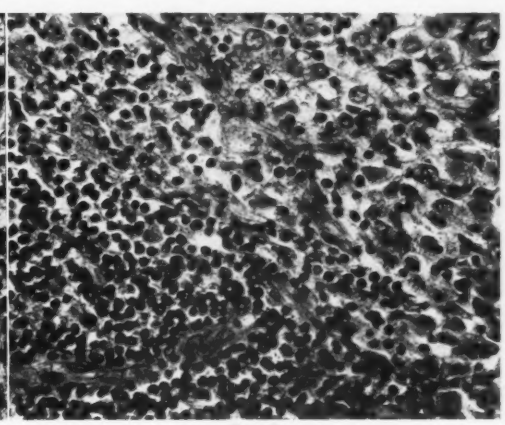

FIG. 7.

FIG. 6. Case 3. Nonneoplastic ductules surrounded by whorls of undifferentiated tumor cells.
FIG. 7. Case 3. Metastatic axillary node partially replaced by undifferentiated tumor cells. Note resemblance to reticuloendotheliosis.

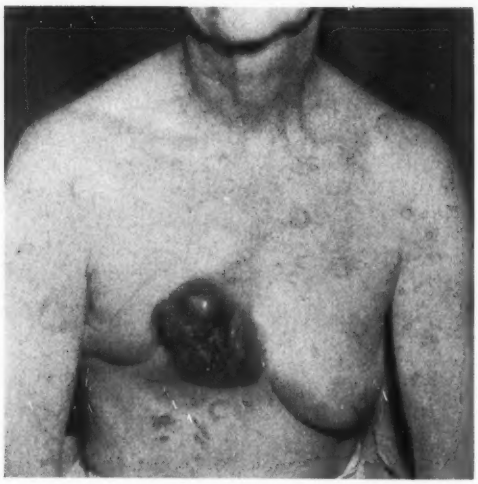

FIG. 8. Case 4. Preoperative photograph of patient.

CASE 3. H. T., a 42 year old white woman, was admitted to the hospital division of the Medical College of Virginia on the service of Dr. Herbert C. Lee on September 6, 1954 for a small nodule in the right breast of 3 years' duration. There was no change in size, but increased firmness and retraction of the nipple had developed 2 years prior to admission. On physical examination a pea-sized nodule was palpable along the lower border of the areola of the right breast. The nipple was retracted. There was no lymphadenopathy. A roentgenogram of the chest was normal. The patient was operated upon on the second hospital day when, following a frozen section report of carcinoma, a radical mastectomy was performed. A course of radiation therapy was started on the thirteenth postoperative day, with a total dosage of 6,500 roentgen units administered. She was discharged on October 6, 1954 and was last seen by her physician in June 1955, at which time there was no evidence of recurrence.

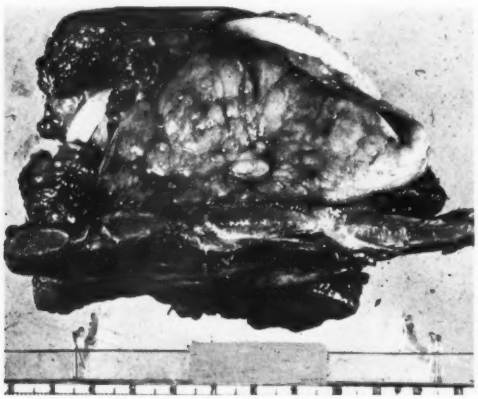

FIG. 9. Case 4. Surgical specimen of radical mastectomy. Sagittal view to show invasion of perichondrium by tumor mass.

The pathologic specimen from the right radical mastectomy measured 20 by 10 by 6 centimeters. There was an ellipse of skin, measuring 10 by 6 centimeters, covering one surface of the specimen. The nipple was partly inverted, with a 3 centimeter recent incision at the inferior border of the areola. Beneath the incision a tumor mass, with a defect due to the previous incision for biopsy, was found. The mass measured 4 by 3 by 1.5 centimeters and was composed of firm, white, gritty tissue with yellowish streaks. Nineteen lymph nodes were dissected from the axillary fat.

At microscopic examination, tumor was found in all quadrants with the exception of the lower outer quadrant. The pectoral muscle was invaded by tumor by direct extension. The tumor pattern was that of individually dispersed cells within the stroma. These sometimes formed linear columns as well as whorls around ductules (Fig. 6). A lobular pattern could also be found in several areas. Two lymph nodes showed evidence of metastases. Again, the pattern of reticuloendothelial hyperplasia was simulated (Fig. 7). The diagnosis was carcinoma (lobular, infiltrating type) of the right female mammary gland with metastases to axillary lymph nodes.

CASE 4. P. N., a 63 year old white woman, was admitted to the hospital division of the Medical College of Virginia on the service of Dr. Frank Philip Coleman and Dr. Claude C. Coleman, Jr. on February 8, 1955 with a mass in her right breast of 12 months' duration. She had developed a high fever and noticed a rapid increase in the size of the breast lesion. Approximately 9 months prior to admission the mass was described as "orange-sized" and was ulcerated. The lesion drained seropurulent material, but she refused medical advice. Five months prior to admission the entire right breast seemed replaced by tumor. On physical examination, there was a mass 8 by 9 by 5 centimeters involving almost the entire right breast with superficial necrosis and ulceration. The mass extended almost past the midline of the sternum and was fixed to the underlying muscles (Fig. 8). There was very little tenderness, and no lymphadenopathy was noted. Roentgenograms of the chest and long bones were negative for metastatic tumor. On February 17, 1955, an intercostal node biopsy was negative for tumor. A biopsy of the mass was reported as infiltrating lobular carcinoma of the right breast. On February 24, 1955 a right radical mastectomy with excision of the anterior chest wall and closure of the defect with pedicle grafts was performed. She was discharged on April 10, 1955, and when seen by her physician 3 months later there was no evidence of recurrence.

The pathologic specimen from the right radical mastectomy consisted of the breast and a portion of the chest wall. The breast measured 15 by 25 by 7 centimeters in its maximum dimensions and was covered on one surface by an ellipse of skin 18 by 29 centimeters. A firm, irregular, nodular mass 9 by 9 by 7 centimeters was present in the medial portion of the breast and appeared fixed to the chest wall. It occupied the upper outer quadrant adjacent to the nipple and extended 1 centimeter to the left of the midline. The superficial portion of the tumor was ulcerated over an area 4 by 3 centimeters. On cut section the tumor mass was 14 by 8 by 5 centimeters and was composed of gray-tan glistening tissue, with numerous foci of necrosis. The skin and underlying perichondrium and periosteum appeared involved by tumor (Fig. 9). The chest wall consisted of 6 centimeters of sternum, the xiphoid process, the costal cartilages of the left fifth and sixth ribs, and the proximal portions of the right second, third, fourth, fifth, and sixth ribs. Thirty-one axillary lymph nodes and 1 Rotter's node were dissected from the axillary fat.

On microscopic examination it was noted that tumor had replaced almost the entire breast and had the pattern of a reticulum cell type of lymphosarcoma (Fig. 10). Only rarely was the lobular pattern appreciated. The tumor had infiltrated the pectoral muscle and extended to the perichondrium (Fig. 11). Twenty-two axillary and 1 Rotter's node showed metastatic tumor (Fig. 12). The diagnosis was carcinoma (lobular, infiltrating type) of the right female mammary gland, with extension to skin, nipple, pectoral muscle, and perichondrium of the right costal cartilage, and metastasis to axillary and Rotter's lymph nodes.

CASE 5. N. P., a 39 year old colored woman, was admitted to the Saint Phillip's Hospital on June 8, 1955 because of a "lump" in her right breast of 2 weeks' duration, associated with intermittent dull and sharp pains. There was no nipple discharge. Physical examination revealed a tender, firm, ill-defined, movable mass in the upper quadrant of the right breast superior to the nipple. There was no fixation of the surrounding tissue and no nipple retraction. There were several right axillary lymph nodes, the largest 2 centimeters in diameter, firm, and tender. A biopsy of the axillary mass and frozen section were done on the eighth hospital day. The lesion was reported as carcinoma, and a right radical mastectomy was immediately performed. She was discharged on July 11, 1955 and received x-ray therapy on an out-patient basis. Her last visit to the clinic on August 31, 1955 revealed nothing of note.

The pathologic specimen consisted of a nodule 1 centimeter in maximal diameter and a mass of fibro-

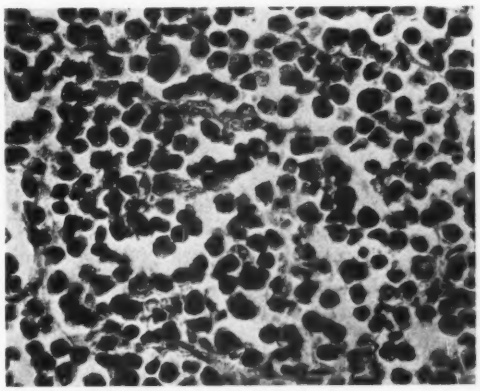

FIG. 10. Case 4. Sheets of undifferentiated cells simulating reticulum cell sarcoma.

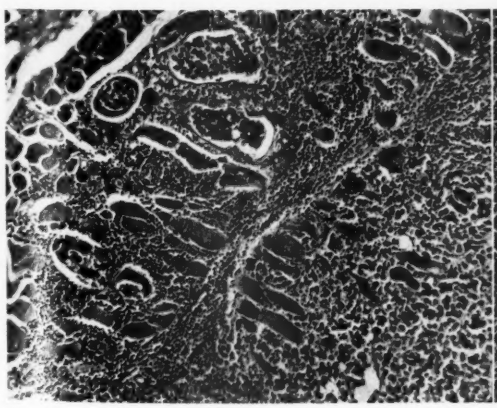

FIG. 11.

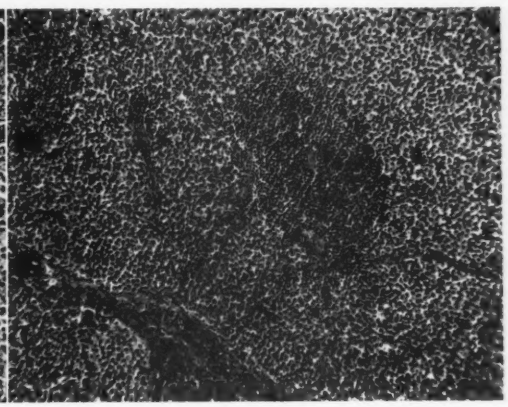

FIG. 12.

FIG. 11. Case 4. Tumor invading pectoral muscle. Note lymphatic vessels filled with tumor cells.
FIG. 12. Case 4. Metastatic axillary node showing superficial resemblance to "sinus catarrh."

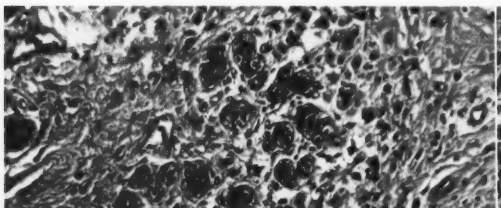

FIG. 13.

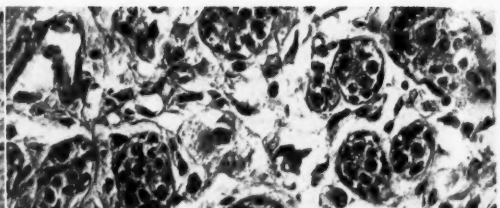

FIG. 14.

FIG. 13. Case 5. An area of lobular carcinoma.
FIG. 14. Case 5. Higher power view of Figure 13. A few neoplastic cells are found free within the stroma.

fatty tissue measuring 3.5 by 2 by 1 centimeters. The latter showed a cystic area filled with soft red grumous material. On microscopic examination the nodule was seen to be a lymph node almost completely replaced by an undifferentiated carcinoma. The tumor was characterized by sheets of large polygonal cells with eosinophilic granular cytoplasm and large nuclei. Only a few scattered lymphocytes were present.

The specimen from the right radical mastectomy measured 28 by 24 by 6 centimeters and was covered by a skin ellipse of 21 by 18 centimeters. The nipple and skin appeared normal and no masses were palpable within the breast. Multiple parallel incisions, however, revealed a hard tumor in the upper half of the breast and beneath the areola. The tumor was approximately 5 by 3.5 by 3 centimeters and was pale gray to pale pink.

Upon microscopic examination, the sections showed tumor diffusely disseminated in the upper quadrants. There was a distinct lobular pattern with many areas of infiltration within the stroma (Figs. 13 and 14). In general, the cells of the infiltrating portion were large and polygonal with bizarre nuclei, occasionally giant-sized (Fig. 15). Twenty-four out of 33 axillary lymph nodes were involved by metastatic tumor. In addition 2 Rotter's lymph nodes were involved. The metastases were similar to that described in the biopsy specimen, but where nodes were only slightly replaced by tumor the tumor cells had the appearance of reticuloendothelial elements (Fig. 16). The diagnosis was carcinoma

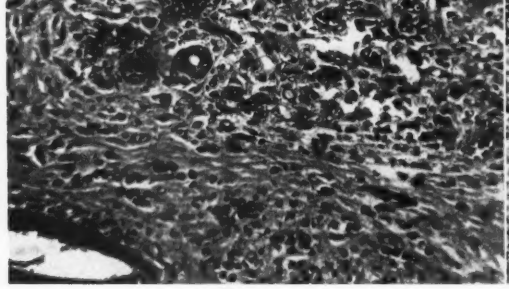

FIG. 15.

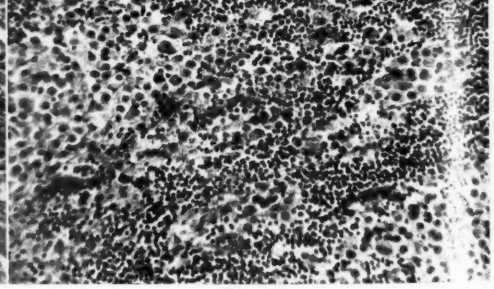

FIG. 16.

FIG. 15. Case 5. An area showing lobular carcinoma with invasion of the stroma.
FIG. 16. Case 5. Metastatic axillary lymph node. The larger cellular elements are all neoplastic.

(lobular, infiltrating type) of the right female mammary gland with metastases to axillary and Rotter's lymph nodes.

COMMENT

The previously described 5 cases were studied with a 5 year period. Actually 4 were seen within the last 2 years, so that follow-up evaluation would be premature. Nevertheless, in all cases, with the exception of Case 2, evidence of axillary metastases was revealed when the major specimens were examined, and it is therefore unlikely that the prognosis would be favorable. This is especially so in those cases in which the nodal metastases were widespread (Cases 1, 4, and 5), the local involvement was extensive (Case 4), and the distant metastases could be demonstrated (Case 2).

Case 1 is of more than passing interest because of the lesion in the left breast, present since 1951. As the original diagnosis was in error, no further surgery was done. Four years later the left breast appeared "normal" on physical examination, but the right breast revealed extensive tumor involvement. Certainly, the disease on the left side was either slow growing or totally eradicated by the local excision, but is the process on the right an autochthonous neoplasm or a metastasis from the left breast? This question is not easily answered as both neoplasms are similar, but it would be more logical to assume that the tumor in the right breast is an entirely new disease in the absence of persistent tumor in the left breast.

Concerning the incidence of this relatively rare neoplasm, it may be repeated that these 5 cases were diagnosed during a period from 1950 to 1955, when there were approximately 332 cases of mammary carcinoma, and, therefore, that they represent an incidence of 1.5 per cent.

Study of the histopathologic changes of infiltrating lobular carcinoma of the breast reveals that often the primary lesion may be quite extensive and not unlike that of lymphosarcoma of the reticulum cell type. In many instances, the tumor may be found in most of the breast quadrants rather than as a circumscribed lesion. If ductules are still well preserved, there is often whorl formation of individual tumor cells surrounding these ductules. The presence of dispersed individual tumor cells within dense fibrous stroma may even superficially resemble fibrous mastitis. Identification of these cells as neoplastic is often difficult even with well prepared permanent sections. Transition changes to an in situ lobular carcinoma are extremely helpful in making the diagnosis of the infiltrating variety. The changes within lymph nodes harboring metastatic tumor are characteristic. Dilated sinuses are filled with individual tumor cells without glandular differentiation. These cells resemble large reticulum cells or histocytes, so that superficially there is a resemblance to reticuloendotheliosis or sinus catarrh.

SUMMARY

Five cases of infiltrating lobular carcinoma of the female mammary gland are presented.

Their histologic features are described, and pitfalls in diagnosis emphasized.

The incidence of this type of lesion is low, representing 1.5 per cent of all mammary carcinomas studied in a 5 year period.

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THE EMERGENCY PORTACAVAL SHUNT

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MARY ANN PAYNE, M.D., New York, New York

MAJOR HEMORRHAGE from esophageal varices presents a prime medical emergency. The loss of blood endangers the life of the cirrhotic patient directly by exsanguination and indirectly by the precipitation of hepatic failure. In a survey of the causes of death in cirrhotic patients, Nachlas, O'Neil, and Campbell reported that hemorrhage was the precipitating or causative factor in 84 out of a total of 88 deaths. The initial hemorrhage itself was associated with a 60 per cent mortality in cirrhotic patients. Not only are repeated hemorrhages a danger to the cirrhotic patient's life but each individual bleeding episode carries its own significant risk.

Adequate treatment of bleeding esophageal varices, therefore, must be directed not only to the prevention of future hemorrhages but to the positive and effective control of active bleeding at the time it occurs. Several methods of treatment of the actively bleeding cirrhotic patient have been proposed. Some of these are designed solely to terminate the emergency situation and permit definitive treatment to be done later under more suitable circumstances. Other measures are definitive in themselves even when performed in an emergency situation. Purely conservative management with blood replacement as the main therapeutic tool, tamponade with the Sengstaken-Blakemore balloon, and direct ligation of the esophageal varices are the chief means of terminating the emergency by temporary control of the hemorrhage. Esophagogastrectomy and portacaval shunt are two surgical measures that can both control the emergency and are definitive in intent. Hepatic artery ligation has been almost universally discarded as an emergency treatment of bleeding varices.

Ideally, temporary emergency measures should be well tolerated by the desperately sick patient, should control the hemorrhage in a reliable and reproducible fashion, and should provide a remission long enough to permit adequate preparation of the patient for definitive surgery.

Rest, sedation, and blood replacement will carry approximately half of the patients who are actively bleeding past their emergency period. Although this conservative regimen avoids the addition of surgical trauma to the desperately ill patient, its salvage rate is too low for reliance to be put in it as an exclusive method of treatment. When successful its success is usually quickly evident as the patient's condition stabilizes and the bleeding ceases spontaneously. When the hemorrhage continues, however, persistence in these conservative measures may prove most unwise. Coma and other evidences of deterioration in hepatic reserve are almost the inevitable result of prolonged or uncontrolled esophageal hemorrhage.

Another method of providing temporary control of the bleeding is esophageal tamponade. The esophageal balloon of Sengstaken and Blakemore has proved to be, in our hands, a most efficient tool for the short term control of esophageal hemorrhage. Almost without exception this balloon will control the bleeding if adequately inflated. Our experiences with its long term use, however, are less happy. Respirations may be hampered by tracheal displacement or, in the young patient with soft tracheal rings, actual tracheal compression may be caused.

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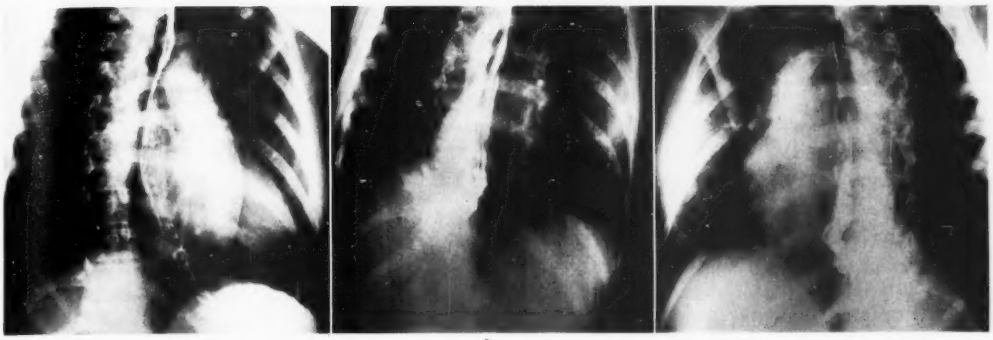

a b c

FIG. 1. D. R. New York Hospital No. 576553. a, Esophagram, July 1950, taken prior to operation. Large esophageal varices are apparent. b, Esophagram of May 1952, 6 months after esophagogastrectomy and esophagojejunostomy. The esophagus is normal and no varices are visible. c, Esophagram of May 1955, 2½ years after operation. Esophageal varices are again present.

Should the balloon rise into the pharynx total obstruction to the airway may result. Atelectasis and pneumonia can and do appear in the debilitated patient in whom total esophageal obstruction is produced. Besides these respiratory dangers, one runs the risk of recurrence of the hemorrhage when the balloon is deflated. This occurs in a significant number of patients, and when it does the patient may well be weaker and a poorer operative risk than before the balloon's insertion. It is in this prompt recurrence of bleeding that we have seen patients lapse into coma and even expire. As with the purely conservative measures prolonged esophageal tamponade is good when it succeeds, but should it fail other measures must be used and used under the most difficult circumstance.

Transesophageal ligation of the varices as recommended by Crile and practiced by Linton is an efficient measure for the control of active bleeding. No permanent control of the bleeding is accomplished and a portacaval shunt within 3 to 4 weeks of the thoracotomy is advised by Linton lest hemorrhage recur and the value of the temporary respite be lost. Linton reports 15 actively bleeding patients treated by ligation of the varices. One patient died postoperatively, 1 died of hepatic failure 6 weeks postoperatively, 5 had recurrent hemorrhages before the portacaval shunt was performed.

The logic of this operation is sound. Direct ligation of the bleeding veins stops the bleeding, terminates the emergency, and permits some time for the proper preparation of the patient for shunt. Yet thoracotomy with esophagotomy is far from a minor procedure. If this operation were of somewhat lesser magnitude and if the postponement of hemorrhage were of a longer duration, this surgical procedure would unquestionably be the one of choice in the management of the actively bleeding cirrhotic patient. However, massive hemorrhage, thoracotomy, and portacaval shunt all within a 4 week period are a not inconsiderable burden for the cirrhotic patient.

Esophagogastrectomy has been performed as both emergency treatment and definitive treatment by Shumacker and King. It is a major surgical procedure with its own inherent mortality and often produces marked disturbances in digestion. Its effectiveness in the emergency control of esophageal bleeding is accepted but, in our opinion, it does not permanently obliterate the esophageal varices or remove the threat of recurrent hemorrhage (Fig. 1). As organic union takes place across the esophagogastric or esophagojejunal anastomosis, the esophageal veins once more unite with the portal tributaries

and share in the portal hypertension. The magnitude of the surgery, the subsequent digestive disturbances, and likelihood of recurrence of the varices combine to make this operation undesirable when other measures are available.

Portacaval shunt is the generally accepted surgical means of preventing esophageal hemorrhage. Its use in the emergency treatment of the actively bleeding patient, however, has not been commonly recommended. Criticism of the portacaval shunt as an emergency measure is based on the high mortality associated with its use under these circumstances. Impressed with the undependability of nonoperative measures for control of active bleeding from esophageal varices and also impressed with the magnitude of palliative and temporary surgical measures, we have considered it proper to utilize the portacaval shunt in the treatment of actively bleeding cirrhotic patients. Initially, this major operation was reserved until it was patently obvious that nonsurgical measures had failed. Temporizing in this fashion we have seen patients deteriorate under nonoperative care, and when the decision to do the portacaval shunt was made, the patient was in desperate condition. As will be seen in the case reports, several patients lapsed into coma during this period of nonoperative care. Yet, despite this fact, some patients operated on within 1 or 2 days after recovery from coma tolerated the procedure well and had no further operations to face in their future. The risk of an emergency shunt seemed to diminish as one considered the danger of watchful waiting on the one hand, and on the other hand the necessity of doing a portacaval shunt later, on those fortunate enough to survive their immediate bleeding episode. In our more recent cases, therefore, the portacaval shunt has been performed as promptly as possible after the institution of esophageal tamponade.

In utilizing the portacaval shunt as an emergency measure only, the two extremes of esophageal bleeders are excluded. First the cirrhotic patient whose hemorrhage is self-limited and who will stop bleeding spontaneously is not considered for emergency surgery. The other extreme is represented by the cirrhotic patient whose hepatic function is such that an early demise is properly predicted even in the absence of hemorrhage.

To exclude the first group our current plan is to treat expectantly but for only a brief time the cirrhotic with esophageal hemorrhage. If the patient ceases to bleed on bed rest, mild sedation, and blood replacement, he is permitted to do so and an elective portacaval shunt is performed later during the same hospitalization. On the other hand, if the bleeding persists or is extreme, the Sengstaken-Blakemore balloon is inserted and the portacaval shunt is performed as soon as the lost blood is replaced and the patient is not in coma. Usually this means operation 24 to 48 hours after the institution of esophageal tamponade.

The other extreme, the patient who is so low in hepatic function that control of hemorrhage will add little to his life span, is recognized as such on admission and nonoperative measures alone are used in his care. The recognition of such a patient does not depend so much on laboratory tests or on his clinical status after the hemorrhage but his general status before the hemorrhage. A worsening of ascites or jaundice or the development of coma after the onset of hemorrhage may be considered an additional reason for controlling and preventing bleeding rather than a contraindication to surgery. In short then, only that cirrhotic patient whose evidence of hepatic failure and downhill course antedate his hemorrhage is refused consideration as a candidate for surgery.

Case 1. G. G., a 54 year old Persian physician who had always abstained from alcohol, was admitted to the New York Hospital in 1950 because of recurrent melena. He had had his first hematemesis in 1938 at the age of 43 years. In 1941, he again vomited blood. Since then he had had 5 episodes of tarry stools, each episode lasting 2 to 3 days. Work-up in 1944 disclosed hepatosplenomegaly, ascites, and esophageal varices. At that time his serum bilirubin was 0.7 milligram per cent, serum proteins 6.3 grams per cent.

After admission to the hospital in November 1950, he had a massive hematemesis and his hemoglobin fell to 8.9 grams per cent. Esophageal tamponade was established, and the lost blood was replaced. The tamponade was effective and after 3 days the balloon was deflated. Bleeding recurred immediately. The balloon was reinflated and left in place for 6 more days, and then removed. A massive hemorrhage occurred the next day. Once again the balloon controlled the bleeding but this time the patient lapsed into coma. This deep coma persisted for 5 days. As soon as his mental state cleared, an end-to-side portacaval shunt was performed, November 24, 1950, with the inflated esophageal balloon in place. He had received 6,500 cubic centimeters of blood before operation and his hemoglobin level the day of operation was 13.2 grams per cent. His portal pressure was reduced by the shunt from 45 to 28 centimeters of saline. Eight days after operation the balloon was removed and his diet was gradually increased. His course in the hospital was satisfactory, and he was discharged 19 days after operation.

Four months later he suddenly became jaundiced, his serum bilirubin rising to 30.2 milligrams per cent. A clinical diagnosis of homologous serum jaundice was made and conservative treatment was given. His recovery was good, and a year postoperatively he was without ascites or esophageal varices. His hepatosplenomegaly persisted. Bleeding never recurred. The patient then left the New York area and died of hepatic insufficiency 16 months after his portacaval shunt. At autopsy the shunt was patent, there were no varices.

This patient is of interest for several reasons. While under our observation he had 3 major hemorrhages, each of which was effectively controlled by the esophageal balloon. However, after each bleeding episode his hepatic reserve was lessened and after the third he was comatose. Never a good operative risk, he became a poorer one after each hemorrhage. Nothing was gained by the delay. The longer operation was postponed, the more his hepatic function deteriorated. Under our current policy the operation would have been performed more promptly when the patient was in better condition.

Despite the fact that this man at the time of operation was such a poor risk, he not only survived the operation, but was able to withstand a severe bout of homologous serum jaundice 4 months later. This occurrence undoubtedly damaged his already diseased liver and shortened his span of life.

CASE 2. E. D., a 40 year old woman with known xanthomatous biliary cirrhosis, was transferred to the New York Hospital on February 14, 1951 because of hematemesis. Her illness began in 1945 with generalized pruritus and skin discoloration. That same year she became pregnant and a hysterotomy and tubal ligation were performed elsewhere.

In 1948 obvious icterus appeared. In October 1950, she vomited blood for the first time. Four months later she was admitted to another hospital with her second hemorrhage. After admission she went into shock and the esophageal balloon was inserted. Twice it was deflated, each time a gross hemorrhage occurred. She was then transferred to the New York Hospital with the inflated balloon in place.

On admission she was jaundiced, her skin was brown, and numerous xanthomatous nodules were present. The liver was enlarged and there was ascites. Laboratory data were as follows: hemoglobin 10.5 grams, bilirubin 6.0 milligrams per cent, total serum protein 7.0 grams per cent, albumin 4.1 grams per cent, globulin 2.9 grams per cent, prothrombin time was normal.

The portacaval shunt was accomplished the day after admission, with the balloon still in place. Her portal pressure was reduced from 46 to 26 centimeters of saline. Before operation, 3,500 cubic centimeters of blood had been administered.

The balloon was removed soon after the operation, and the patient did well. She was discharged on her thirteenth postoperative day. She continued to do well until she was readmitted 1 year later with intestinal obstruction. At operation the obstruction was found to be caused by an adhesion which was lysed. The portal pressure at this operation was 16.5 centimeters of saline. Following operation the patient was comatose for 2 days, but after this she improved steadily and left the hospital 13 days after operation.

Her liver function continued to be adequate and she did not bleed. However, 20 months after the shunt the patient developed, clinically and radiographically, an active duodenal ulcer. This lesion persisted and remained symptomatic. She came under the care of another institution where she died July 22, 1954, 3 years and 5 months after her portacaval shunt. At autopsy the liver was nodular and diffusely cirrhotic. The shunt was patent. There was a duodenal ulcer.

The temporary effectiveness of the esophageal balloon is again illustrated by this case. Yet, each time the balloon was deflated the bleeding recurred. Without portal decompression her survival seemed doubtful. Her survival for 3 years 5 months following the shunting procedure demonstrates that her hepatic reserve was adequate if not sub-

jected to severe strain. It is of interest that 1 year later she did go into coma following lysis of an adhesion but recovered to live another 2½ years of normal existence.

CASE 3. F. M., a 53 year old man with no history of alcoholism but with an occupational exposure to carbon tetrachloride, was admitted to the New York Hospital on December 4, 1952, because of hematemesis. His illness had begun with the abrupt appearance of ascites 1½ years previously. Exploratory laparotomy was performed at another hospital and a cirrhotic liver was found. One year before admission he had his first hemorrhage, was hospitalized, and quickly recovered. When he bled again he was brought to the New York Hospital and admitted. On admission he was not in shock; the liver and spleen were enlarged and ascites was present. Laboratory data were: hemoglobin 10 grams, hematocrit 35 per cent, bilirubin 2.7 milligrams per cent, serum proteins 6.0 grams per cent, albumin 4.0 grams per cent, globulin 2.0 grams per cent, prothrombin time normal.

The esophageal balloon was passed and inflated, and blood administered. Two days after admission the balloon was deflated, he began to bleed again, and lapsed into coma. Tamponade was reinstituted and more blood administered. Gradually his mental state cleared and after 4 days the balloon was removed. Three days later he had another major hemorrhage. The balloon was again passed and after a 48 hour period of stabilization a portacaval shunt was performed on December 16, 1952, with the balloon in place. Prior to operation, 10,500 cubic centimeters of whole blood had been given. His portal pressure was reduced from 39 to 22 centimeters of saline. Postoperatively a wound infection developed and for a while an intraperitoneal mass was palpable in the left abdomen. This disappeared and he was discharged 18 days after operation.

In the out-patient department the mass reappeared in the left midabdomen. He was readmitted and an infected loculation of ascitic fluid was drained in February 1953. No foreign body was present. After this, the patient did well. His ascites did not recur and he gained weight and strength until April 1953, 4 months after the portacaval shunt, when he had a sudden onset of nausea, vomiting, and fever followed by the appearance of progressive jaundice. His serum bilirubin rose after admission to 22.1 milligrams per cent, and he became comatose and expired. The clinical diagnosis was homologous serum jaundice superimposed on hepatic cirrhosis. At autopsy there was widespread nodular cirrhosis. The shunt was patent.

In reviewing this history, it is apparent that the clinical state of the patient deteriorated with each major bleeding episode. While it is always impossible to predict what will happen if the balloon is deflated, in this case it was clearly established after the second hemorrhage, followed as it was by a period of coma, that the consequences of subsequent hemorrhages might be fatal. The risk of deflating the balloon for the third time in this patient, therefore, was a grave one and the hope of obtaining much time for ideal preparation was slight. Our present regimen would be to proceed directly with the shunt on the first episode of bleeding thus sparing him the period of hepatic decompensation. It is again worth noting that despite ascites and coma, this patient was able to withstand the operative trauma. His complicated course was an unfortunate additional strain which exceeded his reserve and he succumbed to the serum jaundice 4 months later.

CASE 4. R. S., a 58 year old woman with a heavy alcoholic history, was admitted to the New York Hospital on December 17, 1952, with a history of 2 weeks of hematemesis, tarry stool, and profound weakness. On admission, her blood pressure was 100/70, pulse 96 per minute. Jaundice, ascites, and hepatosplenomegaly were evident. Laboratory data were: hemoglobulin 3.5 grams, hematocrit 12 per cent, bilirubin 3.2 milligrams per cent, serum protein 5.8 grams per cent, albumin 2.9 grams per cent, globulin 2.9 grams per cent, prothrombin time elevated 2 seconds over the control.

Esophageal tamponade was instituted immediately and blood transfusion given. Despite control of the bleeding, she lapsed into coma, her ascites and jaundice worsened. On the ninth hospital day the patient vomited up the esophageal balloon. For 6 days she did not bleed and her general condition improved slightly until again she began to bleed. The esophageal balloon was replaced and a portacaval shunt was performed January 5, 1953. Five thousand cubic centimeters of whole blood and 1,250 cubic centimeters of packed red cells had been administered before operation. Her portal pressure was reduced from 30 to 20 centimeters of saline. After operation she went into renal failure and died on her fifth postoperative day. At autopsy an advanced cirrhosis was noted. The shunt was patent.

This woman had been bleeding at home for 2 weeks prior to coming to the hospital, and on admission her hematocrit was 12 per cent. This, in itself, was an adequate trial of

waiting for the bleeding to stop spontaneously. While the ascites, jaundice, and coma indicated the precariousness of her hepatic reserve, in retrospect it would seem that this patient may have had a better chance of survival if her shunt had been done as soon as her bleeding was controlled. Certainly, removal of the balloon tamponade without decompression of the portal circuit had little chance of success. We do know from our own experience that a certain number of these severely decompensated patients are salvable.

CASE 5. V. T., a 43 year old woman, was admitted to the New York Hospital on December 18, 1953 because of hematemesis. For 6 years this patient had been troubled by easy fatigability and anorexia. Her alcoholic intake was high, her dietary intake poor. Four years before admission she was transfused because of anemia. Ten months before this admission she had been hospitalized because of hepatosplenomegaly, ascites, and jaundice. At that time her esophagram was suggestive of varices. Her diet was increased and she seemed to be doing well until the morning of admission when she vomited blood several times and had several tarry stools. On admission she was in shock with a blood pressure of 80/40, pulse of 120. The enlarged liver and spleen could be felt, both ascites and jaundice were present. Laboratory data were as follows: hemoglobin 9.5 grams, red blood count 2.0 million, hematocrit 18 per cent, serum bilirubin 3.7 milligrams per cent. Total serum proteins 6.2 grams per cent, albumin 3.6 grams per cent, globulin 2.6 grams per cent. Prothrombin time was elevated 3 seconds over the control.

The esophageal balloon was inserted and inflated and blood replacement begun. Her shock was quickly corrected but on the third hospital day she went into coma. The balloon was deflated. She again vomited blood and the esophageal tamponade was reinstituted. By the fifth hospital day she had received 3,400 cubic centimeters of whole blood and was out of coma. She was still jaundiced and had marked ascites. However, at this time, December 23, 1953, with the balloon in place a portacaval shunt was performed. Her portal venous pressure was reduced from 42 to 30 centimeters of saline. The esophageal balloon was removed on the second postoperative day and feedings were begun. Because of reaccumulation of ascitic fluid, 8,000 cubic centimeters of peritoneal fluid were removed by a paracentesis on the twentieth postoperative day. Three days after this she again became disoriented but quickly regained a clear mental state and was discharged on her twenty-eighth postoperative day. She has done well since then and is essentially asymptomatic in the 20 months since operation. Despite ascites, jaundice, coma, and massive hemorrhage this patient has been salvaged and has gone 20 months since operation and is in good condition.

This was a desperately ill patient who had all of the signs of liver failure, jaundice, ascites, and coma. It is very doubtful if she would have survived her persistent bleeding without esophageal tamponade, and equally doubtful that the bleeding would not have recurred without portal decompression. To operate upon her was a serious responsibility in view of her precarious status. However, we believed that this treatment offered her the one chance of survival at that time and elected to try to help, fully realizing that we might well have lost. We believe that this patient has been salvaged from the group previously considered to be inoperable. She is still in good condition after almost 2 years.

CASE 6. E. M., a 16 year old Puerto Rican girl, was transferred to the New York Hospital from another hospital on March 12, 1954 because of esophageal bleeding. Her illness began at the age of 12 years, in 1950, when she developed jaundice and anorexia. The jaundice waxed and waned over the next several years and 1½ years before admission ascites appeared transiently. One month before her New York Hospital admission she had a hematemesis which was controlled with the esophageal balloon. Several days after its removal, however, she again bled and the balloon was replaced. Active bleeding continued during this month in the other hospital and she was then transferred to New York Hospital for surgery. At the time of admission, she was comatose responding only to painful stimuli. The pressure in the esophageal balloon was increased and the bleeding ceased. Laboratory data were as follows: serum bilirubin 5.4 milligrams per cent, total serum protein 6.7 grams per cent, albumin 2.5 grams per cent, globulin 4.2 grams per cent, prothrombin time increased 7 seconds over the control. With effective esophageal tamponade and blood replacement the patient emerged from coma. She was immediately taken to the operating room and an end-to-side portacaval shunt was performed on March 14, 1954. Her portal pressure was reduced from 38.5 to 14 centimeters of saline. Before operation this girl had received 5,000 cubic centimeters of whole blood.

The esophageal balloon was removed the day after operation and bleeding did not recur. Initially she did well, but about the sixth postoperative day progressive ascites developed and she failed to respond to salt restriction and human serum albumin. She was

transferred back to the original hospital on her nineteenth postoperative day. She continued to fail and expired 1 month after operation. At autopsy her shunt was patent. The liver was the site of severe cholangiolitic cirrhosis as well as extensive endophlebitis and periphlebitis of the hepatic veins.

This young girl was bleeding for 1 month prior to her admission to New York Hospital despite the use of the esophageal balloon. After admission the pressure within the balloon was increased and the bleeding controlled. Here again a long period of waiting was not accompanied by spontaneous cessation of bleeding. Her immediate response to operation was good despite preoperative ascites, jaundice, coma, low serum albumin, seriously elevated prothrombin time as well as prolonged massive hemorrhage.

The bleeding was controlled, but she succumbed 1 month after operation with intractable ascites. At autopsy her hepatic veins were found seriously diseased and her liver contained little functioning tissue. We believe that portal decompression here again offered this young girl her only chance of survival. Unfortunately, her hepatic reserve was so low that she was unable to carry on despite the control of bleeding. We believe that without operation she would most likely have died of hemorrhage.

Case 7. S. R., a 38 year old woman, was admitted to the New York Hospital for the fourth time in March 1954 with a history of 2 seizures of hematemesis, one 3½ weeks before admission, one the day of admission. Three years before admission she had had the onset of fatty food intolerance quickly followed by anorexia, pruritus, and jaundice and the appearance of a widespread skin eruption. Her first admission had been in November 1951 with these symptoms. At that time her liver edge was 4 centimeters below the right costal margin, the spleen 2 centimeters below the left costal margin. There was no ascites and the esophagram was negative for varices. Laboratory data were as follows: hemoglobin, 12.1 grams per cent, red blood count 4.0 million, serum protein 6.8 grams per cent, an albumin of 3.3 grams per cent, a globulin of 4.7 grams per cent, serum bilirubin 6.8 milligrams per cent, 4.6 milligrams per cent being in the direct fraction; alkaline phosphatase 35.5 units, thymol turbidity 12 units, total lipids, 3,640 milligrams per cent with a phospholipid level of 2,690 milligrams per cent. Prothrombin time was normal. The stools were negative for occult blood.

Because of the obstructive nature of her jaundice, exploratory laparotomy was performed and a wholly normal biliary tree was found. The diagnosis of primary biliary cirrhosis was considered established. Shortly after discharge she was readmitted for a minor wound infection. Her jaundice and associated symptoms continued. Her third admission, in 1953, was for dental extractions. Also in 1953, for the first time esophageal varices were seen on x-ray examination.

Her condition remained stationary until the hematemesis which brought about her admission on March 8, 1954.

On admission the patient was in shock, blood pressure 100/50, pulse 100. Her jaundice, xanthomatosis, and hepatosplenomegaly were as before. Her hemoglobin was 5 grams per cent, red blood count 2.6 million. Other laboratory data included serum bilirubin 18.8 grams per cent, alkaline phosphatase 62.4 Bodansky units, cephalin flocculation 7 units, bromsulfalein retention 48.7 per cent, total serum protein 7.6 grams per cent, with albumin 4.5 grams per cent, globulin 3.1 grams per cent. The prothrombin time was normal.

The Sengstaken-Blakemore balloon was inserted at once and 2,750 cubic centimeters of whole blood were administered that day and night. The next day she was out of shock and her hemoglobin was 12.5 grams. A portacaval shunt preceded by a splenoportal venogram was performed the day after admission, March 9, 1954. The esophageal balloon was removed the following day and she left the hospital 18 days after operation. There has been no subsequent bleeding.

This patient has biliary cirrhosis with a high serum bilirubin and high alkaline phosphatase level. Operation was performed promptly with the bleeding controlled by balloon tamponade. Her recovery was uneventful, and she is well today, a year and a half postoperatively. We believe that the prompt handling of this patient saved her further strain from repeated hemorrhage and that this case illustrates the value of proceeding with definitive therapy for esophageal bleeding as soon as the patient has stabilized after hemorrhage.

Case 8. F. A., a 38 year old man, was transferred to the New York Hospital on December 10, 1954 because of esophageal hemorrhage. His first bleeding episode had occurred 5 months previously and had subsided on conservative management and blood replacement. Shortly thereafter, he became jaundiced. Two more severe hemorrhages occurred. He was hospitalized elsewhere and was again treated conservatively. However, this time he continued to bleed

while in the hospital and so was transferred to the New York Hospital. He was deeply jaundiced, had ascites and hepatosplenomegaly. Esophageal varices were seen on x-ray examination. Laboratory data were as follows: Hemoglobin 7.5 grams, hematocrit 24 per cent, serum bilirubin 42.8 milligrams per cent, total serum proteins 6.1 grams per cent, albumin 3.9 grams per cent, globulin 2.2 grams per cent. Prothrombin time was normal.

Initially the patient was not actively bleeding. He was frequently transfused with whole blood and packed red blood cells. However, on the tenth hospital day he began to bleed massively. The esophageal balloon was passed. He became completely disoriented and uncontrollably violent. A tracheostomy was made to relieve possible hypoxia and to prevent any tracheal aspiration. Three days after the tracheostomy he was mentally clear and 3 days later, December 28, 1954, an end-to-side portacaval shunt was performed, reducing his portal pressure from 50 to 38 centimeters of saline. Before operation, 5,500 cubic centimeters of whole blood and 2,000 cubic centimeters of packed red cells had been administered in the New York Hospital. Initially he did well after operation, was alert and comfortable, but on the third postoperative day he began to bleed and bled intermittently thereafter, despite the esophageal balloon, until he died on the seventeenth postoperative day. At autopsy the liver was the site of proliferative endophlebitis of the hepatic veins, and the portacaval shunt was occluded by a thrombus.

The fatal outcome in this patient was the result of failure to decompress the portal system adequately. Despite the extreme degree of jaundice, serum bilirubin level of 42.8 milligrams per cent, and other evidences of hepatic decompensation, coma, and ascites, this man did well for the few days after operation until he bled again.

Tracheostomy was most valuable in the care of this man. The esophageal obstruction and coma made tracheostomy mandatory.

CASE 9. W. D., a 49 year old commercial artist, had imbibed an average of 1 quart of whiskey a day for 14 years prior to his first New York Hospital admission. For an equal length of time he had suffered with gouty arthritis, which had been treated with many medications, including butazolidin and cholchicine. His first New York Hospital admission was in January 1954, for his first episode of bleeding, hematemesis, and melena. Five months later, he again bled and was transfused with 5,000 cubic centimeters of whole blood. A gastrointestinal series at this time was interpreted as showing prolapse of the gastric mucosa. An ulcer diet was prescribed. Gastrointestinal bleeding necessitated 2 more hospital admissions and transfusions.

On August 23, 1954, a subtotal gastric resection was done. No ulcer was found. The omentum was very vascular and adherent to the scar of a prior cholecystectomy. The liver was considered to be mildly cirrhotic, and the spleen slightly enlarged. A pressure reading was taken in a portal tributary and was 25 centimeters of saline.

In the next 12 months, he was admitted to the New York Hospital 7 times for gastrointestinal hemorrhage. Following his admission, August 31, 1955, for melena, he vomited 1,000 cubic centimeters of blood, and the Sengstaken-Blakemore balloon was inserted with quick cessation of bleeding. He had received 8,500 cubic centimeters of blood by transfusion on this admission.

Varices had not been demonstrated on routine gastrointestinal series, and his liver function tests were essentially normal. His liver was 1 fingersbreadth below the right costal margin, the spleen was not palpable.

The patient was first seen in consultation September 6, 1955. The esophageal balloon was in place and the patient's general condition was stable. The following day after a splenoportavenogram was made, an end-to-side portacaval shunt was established. The approach was through a right thoracoabdominal incision and no attempt was made to dissect into the vascular adhesions or omentum, hence no pressure readings were obtained. The anastomosis was 2 centimeters in its longer diameter.

Except for an exacerbation of his gouty arthritis, his postoperative course was smooth. The esophageal balloon was withdrawn without incident the day after operation, and feedings begun soon afterward. He has remained well since that time.

This man, except for his loss of blood, was in good condition compared to the others in the series. However, with procrastination, some deterioration in hepatic reserve might have ensued. Prompt surgical intervention after esophageal tamponade permitted rapid, uncomplicated recovery.

SUMMARY

Nine patients have been subjected to emergency portacaval shunts in the New York Hospital-Cornell Medical Center. In each instance temporary hemostasis had been achieved by the use of the Sengstaken-Blakemore balloon. Seven of these 9 had ascites, 6 had jaundice (serum bilirubin over 3 milligrams per cent), and 6 had been

in coma prior to operation. Three patients died postoperatively, a surgical mortality of 33 per cent. One patient died of hepatic renal failure 5 days after operation, and 1 died a month postoperatively of hepatic failure and hepatic vein obstruction. The third died of unrelenting hemorrhage with a thrombosed portacaval anastomosis.

Of the 6 who survived operation, 3 have subsequently died. In 2 of these 3 deaths it is believed that homologous serum jaundice played a major role. One man succumbed to his homologous serum jaundice and died 4 months postoperatively (Case 3). Another man survived an attack of homologous serum jaundice and died of hepatic failure 18 months after operation (Case 1). The third, a woman, lived 3 years and 5 months after portacaval shunt before dying of hepatic failure (Case 2). The remaining 3 patients are well, although 1 is only recently postoperative. There has been no instance of esophageal hemorrhage in those who survived operation.

In evaluation of these surgical results, we have tended to consider our salvage rate rather than simply our surgical mortality. With no surgical treatment or with a limited surgical procedure, it does not seem likely that a higher survival rate would have been achieved.

The immediate survival of 6 out of these 9 desperately ill cirrhotic patients is not unsatisfactory. With the current plan of management, prompt performance of a portacaval shunt when the hemorrhage necessitates esophageal tamponade, we should avoid the deterioration which follows unsuccessful expectant treatment. By earlier operation, an improvement in the mortality is expected. We believe that portacaval shunt should be considered as an emergency measure for the control of esophageal hemorrhage.

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CARCINOMA IN SITU OF THE UTERINE CERVIX

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THE PRESENT REPORT on 53 cases of carcinoma in situ of the uterine cervix represents part of a 5 year program of clinical, cytologic, and histologic study and follow-up of carcinoma of the cervix in a large and uniform population. It was carried out by the senior author in Puerto Rico in the Department of Health and Medical School, under financing by grants from the National Cancer Institute. Over 8,500 women from the general population were screened by pelvic and cytologic examination. In all of the cases reported suspicious by these methods, biopsies were made. A total of 67 cases of carcinoma in situ were found. Fifty-three of these cases were followed by repeated clinical, cytologic, and biopsy examinations up to 3 years, as yet without any evidence of invasion.

CANCER CONTROL PROGRAM IN PUERTO RICO

Cancer accounts for 4.7 per cent of the deaths in Puerto Rico and is the fifth most frequent cause of death. In the continental United States cancer is the second most frequent killer accounting for 13.6 per cent of deaths. In Puerto Rico the female genital organs are the site of origin of 39.7 per cent of all cancers. This incidence has been calculated by the American Cancer Society to be approximately double that in the continental United States.

Meigs has reported that carcinoma of the cervix constitutes 65.7 per cent of cancers of the female genital tract, with a ratio of uterine body to cervix of 4 to 1. In Puerto Rico an island-wide survey showed that 78 per cent of cancers of the female genital tract arise in the cervix, with a uterine cervix tc corpus ratio of approximately 19 to 1 (Table I). One per cent of these cervix cancers are carcinoma in situ. It should be noted that 75 per cent of the cases of invasive cancer of the cervix, found in an initial island-wide hospital record review were in stages 3 or 4 at the time of the first examination by a medical examining facility. No cytology methods were used in the diagnosis of these cases. Significantly, 100 per cent of the carcinomas found as a result of cytologic examination in the study group of 8,500 women were in stage 1 when demonstrated to be invasive. The patients included in this cytologic study represent a cross section of adult Puerto Rican women from the general population not under medical observation for pelvic symptoms or disease.

Expenses for establishing the cytology program were accurately determined (5). Costs of staffing and equipping the clinic were $6,552.34 while laboratory expenses were $7,674.21. This totaled $14,226.55 for initiating the Cytology Center.[1] It is capable of reviewing 1,000 patients monthly with full outpatient pelvic review as indicated. The laboratory can screen adequately 2,000 slides monthly.

To operate the program 1 year, expenses were $7,582.73 for the clinic and $8,382.76 for the laboratory, totaling approximately $16,000.00.

It was found that yearly screening costs for a total of 6,600 patients with 13,302 cytologic specimens and 228 biopsies averaged $2.40 per patient screened, or a cost of $430.00 per neoplasm discovered. This in no way suggests additional benefits of screening

From the Cancer Program of the Government of Puerto Rico; and the Wayne County General Hospital, Eloise, Michigan. This investigation was supported by a grant from the National Cancer Institute of the United States Public Health Service.

[1] A detailed breakdown of equipment and materials and their cost may be obtained from the author.

TABLE I.—SITE OF 1,380 CANCERS OF THE FEMALE GENITAL TRACT

Site of carcinoma	*No. of cases*	*Per cent*
Cervix uteri	1073	77.8
Corpus uteri	56	4.0
Chorionepithelioma	8	0.6
Uterus, unspecified	104	7.5
Parametrium	63	4.6
Other female genital organs	76	5.5

with no cost for discovering nonmalignant pelvic disease in many patients.

RESULTS

In screening these patients by cytologic methods, findings were reported as: (1) abnormal, not cancer, that is, infection, hyperestrinemia, atypical cells, bloody; (2) suspicious; (3) carcinoma in situ; or (4) cancer, either squamous or other type. An abnormal smear was found in 37.5 per cent. Of these, 88 per cent, or 33.1 per cent of all cases, had an abnormal cytologic pattern regarded not cancer. Abnormal patterns in this group resulted from infection or hyperestrinemia, or consisted of atypical cells and smears unsatisfactory for interpretation often due to admixture with excessive blood. Cytologically, 3.3 per cent of all cases were found to be suspicious of cancer, 0.51 per cent were regarded as carcinoma in situ, and 0.63 per cent were reported as carcinoma (Table II).

In all of the suspicious cases biopsies were made (Table III); in other words, 584 patients were subjected to 1 or more biopsies of the cervix. In 461 of these, no malignant condition was observed. Thus, by combining clinical, cytologic, and histologic means of study, in 98.7 per cent of the total number screened no malignant condition was noted.

Various nonmalignant abnormalities were encountered in the biopsy series (Table IV).

TABLE II.—CYTOLOGY

	No. of cases	*Per cent of abnormal*	*Per cent of total cases screened*
Abnormal pattern, not cancer*	2771	88.0	33.1
Suspicious	282	8.9	3.3
Carcinoma in situ	43	1.4	.51
Squamous carcinoma	53	1.7	.63
Total	3149	100.0	37.5

3,149 abnormal initial smears in 8,379 screened.
*Infection, hyperestrinemia, atypical cells, bloody.

The most difficult and controversial pathologic group is that of the atypical hyperplasias, wherein no fully established microscopic criteria are as yet generally agreed upon to distinguish them. These patients are being examined monthly and biopsies repeated at periodic intervals of not more than 1 year in order to determine their course and ultimate fate while untreated.

Sixty-seven cases of carcinoma in situ were proved histologically, a frequency of 0.79 per cent of the entire series. Smears have been repeated monthly and biopsies have been made at 6 month intervals. Fifty-three of these patients have been followed for as long as 3 years, and in none has the carcinoma become invasive while under our observation. In addition, 48 cases of invasive squamous cell carcinoma were found, 4 patients were found to have adenocarcinoma, and 4 other malignant tumors were discovered—a total of 56 invasive malignant tumors, or 0.67 per cent of all patients screened. Of these cancers, 3 were reported on initial biopsy as carcinoma in situ, but an immediate histologic review of further tissue proved the neoplasm to be invasive. If further and immediate study had not been done, these would later have been wrongly regarded as in situ cases which became invasive.

Those who regard carcinoma in situ as a precursor of invasive carcinoma suggest a range of duration of the lesion in its quiescent or noninvasive state up to 10 years. The age range in our series is from 17 to 77 years at time of diagnosis. The number followed untreated in each decade is indicated in Table V. The average age of patients in this series of carcinoma in situ is 42.9 years. That of Puerto Rican women with invasive cervix carcinoma is 49.2 years, as opposed to the average age of 52.0 years for all female cancer patients in Puerto Rico.

CYTOLOGIC SCREENING

It is practically impossible accurately to diagnose or predict by clinical examination alone the presence of carcinoma in situ, in

spite of the clinician's experience or the use of such diagnostic adjuncts as the Schiller iodine test. Cytologic screening, followed by biopsy of suspicious cases, is essential. There is no uniform method of cytologic reporting for clinical use, and no universally accepted method of interpolation from one system of classification to another. Such items are a requisite if comparable data are to be developed in the study of this problem. The simple method herein presented has proved very satisfactory in this survey from a clinical standpoint.

Blanco developed a system designed to distinguish cellular elements and staining properties with some emphasis on background areas, combinations of which lead the cytologist to render an opinion. Some such uniform method of reporting would be useful if generally adopted by cytologic laboratories. Generally accepted criteria for microscopic diagnoses and the application of uniform terminology would facilitate collecting more nearly comparable data with more compatible interpretations and greater information from follow-up.

Although not universally embraced by all pathologists and cytologists the histologic criteria for carcinoma in situ have been clearly outlined by Reagan in a number of publications (9). Briefly, these can be summarized as follows: involvement of the entire thickness of the epithelium by (a) loss of polarity of the cells and (b) nuclear morphology characteristic of malignancy, i. e., hypertrophy, hyperchromatism, and variations in size and shape of the nuclei; and abnormal mitotic figures.

HISTOCHEMICAL STUDIES

From a strictly scientific viewpoint it has not yet been conclusively proved that carcinoma in situ is the preinvasive stage of cervical cancer, although it is a widely accepted and logical working hypothesis. As Reagan (8) has shown, up to the present time only about 50 cases have been reported in which invasive cancer has been found subsequent to a previous finding of carcinoma in situ. Otherwise, only an occasional histologic study of this lesion has revealed what was interpreted as early invasion. Fennell reported 8 such cases. The follow-up study reported herein was motivated by the possibility of observing such a transition clinically.

TABLE III.—PATHOLOGY

Biopsy diagnosis	*No. of cases*	*Per cent of biopsies*	*Per cent of cases screened*
Not cancer	461	78.9	
Carcinoma in situ	67	11.5	.79
Epidermoid carcinoma	48	8.2	.57
Adenocarcinoma	4	.7	.05
Other malignancies	4	.7	.05
Total	584	100.0	

584 biopsies from 8,435 screened.

The opportunity of also observing possible histochemical changes in the course of such a transition from carcinoma in situ to invasive carcinoma prompted a special study of 22 of these 53 cases all with previous histologic diagnoses of carcinoma in situ. Additional biopsy material from these 22 cases, consisting of endometrial curettings, endocervical biopsy, biopsy from the portio, and a vaginal biopsy, was fixed in absolute alcohol, and some of the material was fixed in neutral buffered formalin. Microscopically, the additional tissue from 11 of these cases continued positive for carcinoma in situ. Glycogen stains, PAS stains, and stains for alkaline phosphatase were made on the tissue from these 11 cases. The results are summarized in Table VI.

Glycogen and alkaline phosphatase are present in all but 1 of these 11 cases of carcinoma in situ, although in decreased and varying amounts. It is possible that cyto-

TABLE IV.—NONMALIGNANT ABNORMALITIES

	No. of cases	*Per cent of biopsy cases*	*Per cent of patients screened*
Hyperplasia	25	4.3	.29
Anaplasia	7	1.2	.08
Metaplasia	8	1.3	.09
Dysplasia	0	0	0
Dyskeratosis	0	0	0
Hyperkeratosis	2	0.3	.02
Epidermization	57	9.7	.67
Squamous metaplasia	45	7.8	.53

584 biopsies from 8,435 screened.

TABLE V.—AGE DISTRIBUTION OF PATIENTS WITH CARCINOMA IN SITU

Age group, years	*No. of patients*	*No. of cases of carcinoma in situ*
10 to 19	215	1
20 to 29	1679	1
30 to 39	2887	23
40 to 49	2121	16
50 to 59	1160	8
60 to 69	369	2
70 plus	78	2
Total	8509	53

chemically diminishing stores of glycogen together with its related enzyme systems may indicate dedifferentiation and, therefore, increasing malignancy. Foraker, in a study of 28 cases of squamous cell carcinoma, has demonstrated such decreasing amounts of glycogen in the more undifferentiated areas of the cancers.

ADDITIONAL STUDIES

A study was also made of the cases of carcinoma in situ which were encountered in the course of a review of the histologic sections of 811 cases of carcinoma of the cervix which were accumulated in the files of the Pathology Department of the Wayne County General Hospital between 1932 and 1955. This study is being reported separately (7), but the following is a summary of the results:

Sixteen cases of endocervical neoplasms were found in which the adjacent portio vaginalis was observed to be the site of carcinoma in situ. These include 4 cases of adenocarcinoma; 1 carcinosarcoma; 1 mixed mesenchymoma; 2 cases of adenocarcinoma in situ; 2 cases of grade 3 squamous cell carcinoma, 1 case of grade 2, and 2 of grade 1 squamous cell carcinoma. In all 16 the associated carcinoma in situ was found separate from the endocervical neoplasm.

TABLE VI.—RESULTS IN 11 CASES OF CARCINOMA IN SITU

Case No.	*Glycogen*	*PAS*	*Alkaline phosphatase*
4790	3+	3+	1+
8162	2+	2+	1+
3680	2+	2+	1+
2137	2+	2+	1+
1803	2+	2+	1+
8029	1+	1+	trace
7541	1+	1+	trace
7536	1+	1+	0
4598	1+	1+	trace
3770	1+	1+	trace
2599	0	0	0

These cases suggest that the occurrence of carcinoma in situ reflects a tendency of the involved cervix as a whole to develop neoplasms. Only 1 such case, that of Friedell and McKay, has previously been reported.

This concept is further supported by the following additional cases that were encountered in the Wayne County General Hospital Pathology Department files: 10 cases of carcinoma in situ adjacent to carcinomas of the portio whose histologic patterns were distinctly different and therefore not the result of invasion and spread along the surface by the carcinoma; 6 cases of leucoplakia overlying large areas of carcinoma in situ, in 1 of which early invasion was found; and 1 case in which ample glycogen was found in the carcinoma in situ, but very little in the adjacent grade 2 squamous cell carcinoma. A total of 33 neoplastic processes were found in which an adjacent and separate carcinoma in situ was present.

In an additional 38 cases, carcinoma in situ was also found adjacent to the invasive carcinoma, but was fused with it, so that it was impossible to rule out spread along the surface epithelium by the invasive carcinoma. For the purpose of this study, it was therefore deemed essential to include only those cases in which the two were seen to be distinctly different.

In an additional 20 cases of invasive cervical cancer, atypical hyperplasia of the epithelium of the adjacent portio was observed, but this histologic picture is not at the present time regarded as significant, and much research remains to be done on this problem.

In none of these cases was there a record of therapy with antifolic acid substances which might induce epithelial atypism, as reported by Weston and Guin.

No carcinomas in situ were found associated in 53 cases of carcinoma of the uterine

fundus, 2 cases of choriocarcinoma, and 9 cases of leiomyosarcoma of the uterus which were reviewed.

SUMMARY

1. Carcinoma in situ occurs in .79 per cent of the general population of Puerto Rican women and may be found in all decades of life after menarche.

2. Fifty-three patients with carcinoma in situ have been followed untreated for periods up to 3 years using monthly smears and biopsies at 6 month intervals. So far, there has been no evidence of invasive change. Follow-up is planned to continue in this manner indefinitely unless histologic evidence of invasion develops. To our knowledge, there are available in the world 4 other series of carcinoma in situ being followed untreated: Peterson 52, Stockholm; Kotmeyer 48, Copenhagen; Nieberg 23, Augusta, Georgia; Graham 13, Boston. We urge that these series totaling 189 cases combine data under some authority such as the Inter-Society Cytology Council, thus making all data available to answer many questions presently outstanding, and further studies may continue in a uniform manner.

3. It is shown that the diagnosis of carcinoma of the cervix is more frequently made at an early stage of the disease when cytologic screening is applied.

4. In this study, the average age of the patients with carcinoma in situ was 6.3 years younger than the average age of patients with invasive carcinoma of the cervix. If carcinoma in situ does progress to invasive carcinoma it apparently takes longer than 3 years following diagnosis by the methods of general population screening as shown in this study.

5. Simple suction of the vaginal pool provides adequate specimens for cytologic review and may be done by a nurse or technician. Actual exposure of the cervix and scraping of its surface yields no significant increase in the number of neoplasms. Since cervix exposure is necessarily done by a physician, it does increase the usefulness as well as the cost of screening techniques in discovering other forms of pelvic disease. Certain abnormal hyperplasias are found in any series of biopsies of the cervices in a cross section of adult women. The possible role of these lesions as stages in the evolution of invasive neoplasm has not yet been demonstrated. A series of such entities is being followed untreated to determine their ultimate fate.

6. Agreement of terminology, classification, and interpretation among various systems is needed in clinical, cytologic, and pathologic categories for the study of carcinoma in situ. Methods for developing this agreement are suggested.

7. Clinical judgment, even when aided by such adjuncts as the Schiller iodine test, is wholly unreliable in estimating the presence of carcinoma in situ.

8. Some carcinoma in situ may represent a portion of a reactive or malignant process. It is, therefore, necessary to exclude by careful histologic study actual invasive carcinoma of the cervix, endocervix, or endometrium before definitive treatment is decided upon.

Short of hysterectomy, cervix amputation, or cone (ring) biopsy with serial sectioning of specimens, certainty of the presence of carcinoma in situ uncomplicated by coexistent invasive neoplasm cannot be assured without careful microscopic examination of tissues from: (a) endometrial suction curetting, (b) endocervical canal curettage, (c) squamocolumnar junction multiple punch biopsy, and (d) multiple punch biopsies of the cervix portio. These can be safely done under outpatient clinic conditions.

9. Cytologic screening is an excellent method of selecting from a general population the vast majority of individuals who either have early cancer of the cervix or deserve further study. It is not felt that cytologic evidence alone is sufficient for the institution of definitive therapy.

10. It is possible that diminishing stores of glycogen together with its related enzyme

systems may indicate dedifferentiation and therefore increasing malignancy in carcinoma in situ of the cervix.

11. The presence of carcinoma in situ in the cervix uteri may reflect a tendency of the entire cervix to develop neoplasms.

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SKELETAL METASTASES IN CANCER OF THE BREAST

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SKELETAL METASTASIS is a common manifestation of advanced neoplastic disease of the breast. Due to the frequency of the latter, many such cases are seen in a hospital specializing in the care of patients with cancer. At the Ellis Fischel State Cancer Hospital, Columbia, Missouri, 166 patients of this type were observed in the first decade of operation (1941 to 1951). Fifty-five of the patients had been previously treated by radical mastectomy at this instutition; the remainder had received prior treatment elsewhere or presented clinical evidence of widespread dissemination on initial examination. Diagnosis, in the majority of instances, rests on roentgenologic evidence; in a few cases bone biopsy was performed.

It is emphasized that this was not a predesigned study. Ordinarily, roentgenographic examination of the skeleton was accomplished only when there was clinical indication of the likelihood of involvement. When this situation obtained, the extent of roentgenologic search for metastatic foci varied from a single film to a complete bone survey. It should be noted that many of these cases were studied during World War II when abundant quantities of roentgenographic supplies were not always available. Had complete skeletal surveys been performed in all cases, it is likely that many unrecorded metastatic foci would have been disclosed.

It seems unnecessary to review again the numerous theories relevant to the manner of dissemination; it should suffice to state that all possible avenues have been indicted.

AGE

The age distribution for the entire group of 166 cases at the time of demonstration of skeletal involvement is shown in Table I.

It has been both suggested and denied that age may play a role in influencing the probability of skeletal metastasis in breast cancer.

For purposes of comparison we have contrasted the following groups:

A. Patients subjected to radical mastectomy at the Ellis Fischel State Cancer Hospital who subsequently developed bone metastases (55 cases).

B. Patients subjected to radical mastectomy at the same institution 5 or more years ago, who subsequently presented no clinical or x-ray evidence of skeletal metastases (240 cases).

Since, as will be shown later, 96 per cent of all patients demonstrating bone metastases subsequent to radical mastectomy did so within a period of 5 years, it seems plausible without introducing significant error to compare these two groups on the basis of age at the time of radical mastectomy (Table II).

Although the number of cases is relatively small, the difference is significantly great to suggest that bone metastases are more likely to occur in patients who develop breast cancer at a relatively early age than in more elderly individuals. Perhaps factors related to age but not controlled in this study (such as lymph node metastases, endocrine status, and biologic potential of the tumors) are the actual determining mechanisms, merely operating through this medium.

CLINICAL CHARACTERISTICS OF THE PRIMARY LESION

There is no evidence in the literature that the quadrant localization of the primary lesion has any compelling or restraining influence on its ultimate capacity for bony

From the Ellis Fischel State Cancer Hospital, Columbia, Missouri.

A portion of this work was done as a Clinical Fellow of the American Cancer Society.

TABLE I.—AGE DISTRIBUTION

Age, years	*No. of cases*	*Per cent*
21–30	1	0.6
31–40	23	13.8
41–50	42	25.4
51–60	51	30.8
61–70	32	19.2
71–80	17	10.2
	166	100.0

TABLE II.—RELATION OF AGE TO BONE METASTASES

Age at time of radical mastectomy, years	*Per cent of 55 with bone metastases*	*Per cent of 240 without bone metastases*
	Group A	*Group B*
26–45	34.5	11.2
46–65	45.6	52.7
66–85	19.9	36.1

metastasis. We are unable to demonstrate such a relationship in this series. There is a slight predominance of lesions of the left breast (54 per cent) but this is in accordance with the usual distribution of breast cancer.

The clinical characteristics of the primary lesion were analyzed in the patients operated upon (group A) to determine which feature, if any, was associated with the subsequent manifestation of osseous metastasis (Table III). Such information aids in the delineation of a group in which a preoperative bone survey would be sufficiently productive to justify its routine use. In 9 patients the breast or a portion thereof had been removed elsewhere prior to admission, precluding their incorporation in this section of the study. Comparison is again made with the control group of 240 cases (group B).

LOCATION OF DEMONSTRATED BONE METASTASES

The frequency of involvement of individual bones, as recorded in the literature, is extremely variable. This is due in part to the varying frequency with which a thorough search for skeletal metastases is made (Table IV).

With the exception of the femur, which for obvious reasons cannot be entered into such comparison (Table IV), there is a striking inverse relationship between the number of times a given bone was demonstrated to contain metastases and the number of times no attempt was made. Such a relationship would be anticipated but is not ordinarily considered among the possible explanations of metastatic localization.

TABLE III.—CLINICAL CHARACTERISTICS OF PRIMARY LESION

	Group A, per cent	*Group B, per cent*
Edema of skin of breast	33	12
Ulceration of skin of breast	9	16
Fixation of tumor to skin	85	76
Mass greater than 3 cm.	80	68
Positive axillary nodes	61	45

Table V records the frequency of localization in our own experience and that of others. The mandible and maxilla and the bones of the forearm, leg, and foot were demonstrably involved in only an occasional case.

Although from an academic viewpoint, we have looked with disfavor upon obtaining anything less than a routine skeletal survey, from the more practical standpoint the following fact is of importance; roentgenograms of only the lumbar spine, pelvis (showing the upper femora), and chest (showing the ribs) revealed metastases in 90 per cent of the 166 patients in this series.

PATHOLOGIC FRACTURE

The variable incidence of pathologic fracture as recorded in the literature may be explained in part by the interpretation of the word "fracture," some authors preferring not to include vertebral compression under this heading although most, including ourselves, have done so. The relative proportion of far advanced cases in the population of the hospital from which the report emanates also plays a role since pathologic fracture is most often a preterminal manifestation.

In Copeland and Geschickter's series of 100 cases of bone metastases in patients with breast cancer, 15 fractures occurred (femur 13, ilium 1, ribs 1). Welch found an incidence of 17 per cent in a series of 151 cases. Freid reported fractures in 21 of 81 patients (26 per cent).

TABLE IV.—SCOPE OF ROENTGENOGRAPHIC INVESTIGATION

Site	Postive roentgenogram No.	No roentgenogram taken No.
Ribs	102	1
Pelvis	99	28
Lumbar vertebrae	88	31
Dorsal vertebrae	65	59
Skull	58	65
Humerus	18	141
Cervical vertebrae	12	147
Femur	77*	87

*The majority of these were demonstrated on roentgenograms of the pelvis; films of the femur, per se, were ordinarily not obtained.

In our series fractures were noted in 80 of the 166 patients (48 per cent). In Table VI multiple fractures in the same patient are included only if they occurred in "different" bones, since ribs and vertebrae are considered as a unit in each patient; hence the total in Table VI is greater than 80, but it does not represent the actual number of fractures.

ROENTGENOGRAPHIC TYPE

The relative frequency of the various roentgenographic types of metastases in similar series is presented in Table VII. Our data vary but little from the material previously reported by others.

It has been shown by Sharpe and McDonald that regardless of the roentgenographic appearance there is always an admixture of bone formation and bone destruction on microscopic examination, the roentgenologic features depending upon the dominant process. There is no clear-cut explanation of the determining factor in this predominance; it has been attributed to rate of growth, grade of lesion, and phosphatase content of the metastatic tissue.

RESIDUAL LOCAL DISEASE

We were interested in ascertaining the frequency with which disease remained in or about the breast. We include under the term "residual local disease" the following: primary tumor present, "recurrent" skin nodules, and homolateral axillary, parasternal, or supraclavicular lymph node metastases.

TABLE V.—LOCATION OF DEMONSTRATED BONE METASTASES

	EFSCH Per cent	Sutherland Per cent	Bouchard Per cent	Freid Per cent	Dresser Per cent
Ribs	61.4	21.6	35	39	31
Pelvis	59.6	54.2	45	62	64
Lumbar vert.	53.0	33.1	44	34	50
Femur	46.4	18.1	32	54	—
Thoracic vert.	39.1	7.4	41	24	40
Skull	34.9	7.9	14	35	44
Humerus	10.9	4.6	—	27	—
Sternum	10.9	—	—	1	—
Scapula	9.6	—	—	16	—
Clavicle	9.0	—	—	14	—
Cervical vert.	7.2	2.0	10	8	17
No. of cases	166	393	101	81	134

TABLE VI.—PATHOLOGIC FRACTURE

Site	No.
Vertebra	46
Cervical	0
Dorsal	23
Lumbar	23
Rib	26
Femur	16
Pelvis	4
Humerus	3
Clavicle	2
Mandible	1
Sternum	1

Residual local disease was present in 130 of the 166 cases (79 per cent), absent in 32 (19 per cent), and indeterminate in 4 (2 per cent). Thus, control of the primary lesion or its regional metastases had not been attempted or had failed in the majority of cases in which bone metastases were demonstrable.

ASSOCIATED PULMONARY METASTASES

Paletta and Lehman believe that certain breast cancers have an affinity for skeletal and others for visceral metastases. They recognized this as a clinical phenomenon usually not substantiated by autopsy (at which time involvement of both is more common), but did not believe this observation invalidated their impression.

In Bouchard's series 54.2 per cent also had "pleuropulmonary" metastases. Turner and Jaffe studied 69 cases with bone metastases at autopsy and pulmonary metastases were found in 41 (59 per cent). Warren and Witham's autopsy findings were almost identical.

Our clinical material was analyzed in this respect with the results shown in Table VIII.

TABLE VII.—ROENTGENOGRAPHIC TYPE OF METASTASIS

Author	*No. of cases*	*Osteolytic, per cent*	*Osteoblastic, per cent*	*Mixed, per cent*
Paletta	48	79	4	17
Sharpe	219	97	3	—
Carnett	101	98	2	—
Sutherland	393	96	3	1
EFSCH	166	80	4	16

TABLE VIII.—ASSOCIATED PULMONARY METASTASES

	No. of cases
Pulmonary and skeletal metastases demonstrated simultaneously	42
Pulmonary metastases demonstrated after skeletal metastases	13
Pulmonary metastases demonstrated prior to skeletal metastases	0
Pulmonary metastases questionable	13
Pulmonary metastases not demonstrated	97
Chest x-ray not available	1
	166

Pulmonary metastases were unequivocally demonstrated in only 55 of the 166 patients (33 per cent). The application of these data to the controversy regarding the mode of dissemination while provocative is unwarranted for a number of reasons. The findings are of considerable significance, however, relative to the preoperative investigation of the patient with breast cancer. Today, no surgeon would consider performing a radical mastectomy without prior roentgenographic examination of the chest, yet a preoperative bone survey is not ordinarily obtained. This study demonstrates that the surgeon should not accept a negative chest film as incontrovertible evidence that metastatic disease is nonexistent, as in no case in our entire series did demonstrable pulmonary metastases antedate revelation of osseous metastases although the reverse situation occasionally obtained. In addition, in 24 per cent of those cases in which radical mastectomy was performed at the Ellis Fischel State Cancer Hospital, the bone metastases were demonstrated within 6 months of the time of surgery. This observation suggests that some may have been present at the time of radical mastectomy and might have been demonstrated had the attempt been made.

We believe that in cases of borderline operability, especially when clinically positive axillary nodes are present, the indication for a complete bone survey is sufficiently great to warrant its use; and that in all cases a partial survey to include roentgenograms of the chest, lumbar spine, and pelvis should be obtained prior to surgical intervention.

ASSOCIATED LYMPH NODE METASTASES

The fact that a possible relationship exists between lymph node involvement and skeletal metastasis has received little attention in spite of frequently recurring statements that bone metastases may be the result of lymphangitic spread. In a series of 48 cases with bone metastases presented by Paletta and Lehman, 73 per cent showed evidence (apparently clinical) of lymph node metastasis. The corresponding figure (basis not stated) of Sharpe and his group in 219 cases was 75 per cent. Toumey studied 42 cases of vertebral metastases from primary cancer of the breast. In 22 of these, radical mastectomy had been performed at the Lahey Clinic and in every case involvement of lymph nodes was found by the pathologist on study of the surgical specimen. Burch reviewed 41 patients with bone metastases, all of whom had had radical mastectomy performed at the Mayo Clinic. Thirty-three of these (80 per cent) had axillary lymph node involvement.

In this series of 166 cases, there were 55 patients who underwent radical mastectomy in our institution. Of this number, 49 (89 per cent) had histologically proved axillary lymph node metastases. Of the remaining 6 patients, 2 were subsequently proved to have supraclavicular lymph node metastases; these most likely existed in a subclinical state prior to radical mastectomy. Two patients had medial hemisphere lesions and the possibility of hidden metastases in the internal mammary nodes is not unlikely. In 1 instance it is almost certain as the neoplasm had invaded the pectoral muscle and the intramuscular lymphatics contained tumor. The lesion in the fifth patient was a fibrosarcoma rather than an adenocarcinoma, the only such exception in the series. In

the sixth patient the primary tumor was located in the upper outer quadrant. This was one of our earliest cases and an adequate study of the specimen by our present criteria (Ackerman) was not carried out. Only 7 nodes were examined in contrast to our present average of approximately 30. A more diligent search for nodes might have been rewarding.

It may therefore be stated that the vast majority, perhaps every case of carcinoma of the breast which manifests skeletal metastases following radical mastectomy, will show pathologic evidence of regional lymphatic involvement at the time of surgical removal of the primary lesion. These findings might be improperly interpreted as indicating the lymphangitic nature of skeletal metastases, an invalid conclusion from the material presented. Whether such an invariable association represents a cause and effect relationship is conjectural.

INTERVAL BETWEEN RADICAL MASTECTOMY AND DEMONSTRATION OF BONE METASTASES

In the series reported by Sharpe and McDonald the average time between operation and the onset of osseous symptoms was 15 months. In other series, the interval has varied between 21 and 30 months. In our own, the average time between operation and the actual roentgenographic demonstration of bone metastases was 19.8 months. The distribution of the 55 cases in which radical mastectomy was carried out at our hospital is shown in Table IX.

Attention is called to the fact that it is exceedingly uncommon for bone metastases to become manifest 5 or more years after radical mastectomy.

SURVIVAL AFTER DEMONSTRATION OF BONE METASTASES

In Bouchard's series of 24 cases, the average survival after the appearance of bone metastases was 13.6 months. In the 23 cases reported by Toumey it was 11 months. In Paletta and Lehman's 48 cases, 60 per cent were dead within 1 year, 84 per cent within 2 years, and the entire group within 4 years. Our own experience is presented in Table X.

TABLE IX.—INTERVAL BETWEEN RADICAL MASTECTOMY AND BONE METASTASES

Interval, months	*No. of cases*	*Cumulative per cent*
0–6	13	24
7–12	11	44
13–18	8	58
19–24	7	71
25–36	5	80
37–48	7	93
49–60	2	96
>60	2	100

TABLE X.—SURVIVAL AFTER DEMONSTRATION OF BONE METASTASES

Period, months	*No. of cases*	*Cumulative percentage dead*
0–6	75	50
7–12	30	70
13–18	15	80
19–24	11	87
25–36	15	97
37–48	3	99
49–60	1	100

Average survival 10.7 months

Sixteen patients are still alive, but to date no patient in the entire series has as yet survived 5 years subsequent to the demonstration of bone metastases. Although it is recalled that the majority (111) of these patients were suffering from widespread dissemination at the time of diagnosis, the survival curve for the 55 patients subjected to radical mastectomy at our institution does not differ significantly from the curve for the entire group, i.e., they are superimposed. This is true, even though the bone metastases in the patients subjected to surgery in our hospital were presumably recognized sooner, since all patients were seen at frequent intervals following surgery. If the deceased members of this smaller group are considered separately, it is found that 48 per cent died within 6 months of the demonstration of bone metastases, 60 per cent within 12 months, 77 per cent within 18 months, 89 per cent within 2 years, 98 per cent within 3 years, and 100 per cent within 5 years. Seven of the patients are still alive, the longest survival being for a period of 51 months.

SUMMARY

One hundred sixty-six patients with bone metastases secondary to breast cancer have been studied. Such dissemination occurs with increased frequency in the younger patient and in those with clinical signs of locally advanced primary disease.

Ribs, pelvis, lumbar vertebrae, femur, thoracic vertebrae, and skull, in decreasing order of frequency, are the most common demonstrated sites of metastasis. An anticipated parallel exists between the frequency of roentgenographic observation and roentgenographic demonstration of bone metastases. Pathologic fracture, most frequently vertebrae and ribs, occurred in 48 per cent of the patients. Residual local disease was present in 79 per cent. Lymph node metastases (almost) invariably precede demonstrable osseous involvement.

Pulmonary metastases were demonstrated roentgenographically during the course of the disease in only one-third of the cases. The clinical significance of this fact in the evaluation of the patient for surgical intervention is stressed; the necessity of preoperative roentgenographic exploration is demonstrated.

The average interval between radical mastectomy and actual roentgenographic demonstration of skeletal metastasis was 20 months. Average survival after such demonstration was 11 months.

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ACUTE HEPATIC ISCHEMIA IN DOGS

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STUDIES ON THE EFFECTS OF ISCHEMIA of the liver were retarded by the complex arteriovenous afferent blood supply and by the susceptibility of the ischemic liver to infection. With the advent of a more standardized method of producing portacaval shunts and the increased use of chemotherapy, the greater portion of these obstacles have been overcome. Additional impetus for the information concerning the tolerance of the liver for ischemia has come from clinical medicine. Ischemic liver fields have been used in the surgery of malignant lesions of the liver, and hepatic artery ligation has been used in the treatment of bleeding esophageal varices due to cirrhosis. In addition, the vessels in the hepatic pedicle have been frequently ligated in surgery of acute trauma, and recently, there has been much work relating the hepatic circulation and surgical shock. In the present study, the afferent blood supply to the liver in dogs was ligated for relatively short periods and effect noted as related to survival times, certain liver function tests, and the clinical signs shown by the animals.

REVIEW OF LITERATURE

Haberer in 1905 learned that if the hepatic arteries were ligated in the dog, the animal would die. Huggins and Post confirmed this work and found that if the procedure was carried out in multiple stages some of the dogs survived. While investigating this problem, Markowitz, Rappaport, and Scott in 1948 found that the administration of penicillin prevented death after hepatic artery ligation. This finding was confirmed by Davis, Tanturi, and Tarkington. Ellis and Dragstedt and Markowitz and his associates found that the necrotic livers of dogs dying after hepatic artery ligation abounded with spore-bearing anaerobic rods, and these same organisms are known to exist in the liver of the normal dog. It has been suggested that the hepatic arterial supply is necessary in order to keep the oxygen tension in the liver high enough to prevent the proliferation of the anaerobic bacteria present. Popper (15, 16) believes that if all the arterial supply to the liver is properly ligated, the dogs will die in spite of chemotherapy.

About 75 per cent of the hepatic blood supply and 50 per cent of the oxygen supply are carried by the portal vein. However, it has been known since Eck's experiments in 1877 that dogs will tolerate the occlusion of this vessel when an anastomosis is made between it and the vena cava below the ligature. If the portal vein is simply ligated, the animals will die in about an hour. When the portal system is occluded gradually over a period of 10 days, it was found that about half of the dogs survived because of the formation of collateral circulation.

Rappaport and Lotto (18, 19) produced hepatic coma in dogs by ligating the hepatic arteries 24 to 48 hours after an Eck fistula. The shorter the period of time between the procedures, the more marked the coma. This observation has been confirmed by others. DeWeese and Lewis studied the effect of permanently ligating one branch of the portal vein as it entered the liver, and, at the same time, of temporarily occluding the hepatic artery up to 1 hour. All of the dogs survived and showed very little outward effect, even though no chemotherapy was given. It has been found that some dogs will tolerate a gradual total devascularization of the liver. Some say this is not accounted for in the vascular supply of adhesions or collateral; while others say that this is the reason they survive.

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The first to ligate both the portal and arterial supply to the liver at the same time were Hahn, Maasen, Mencki, and Pawlow in 1893 (as quoted by Rappaport, 18). After production of an Eck fistula and ligation of the common hepatic artery, their dogs lived only 12 to 15 hours, dying of "wet necrosis of the liver." Tinker and Tinker reported the tolerance in the dog for clamping the entire hepatoduodenal ligament to be 15 minutes as the "intestines turned blue" and the animals died. Raffucci and Wangensteen ligated the superior mesenteric artery, portal vein, and hepatic artery for short periods of time and found the maximum tolerance for the procedure was about 20 minutes. However, the tolerance for ischemia of the small intestine itself is about the same time. Bernhard and associates repeated Raffucci's experiment with the liver ischemia being produced under hypothermia (24 to 27 degrees C.) for 1 hour periods. Whereas all the control dogs died, only 2 of 27 died under hypothermia.

METHODS

Forty-one adult mongrel dogs were used, the average weight being 18.7 kilograms. Liver function tests were run 2 days prior to operating upon the animals. Preoperative medication consisted of penicillin 4 hours before surgery and morphine and atropine 1 hour before surgery. The anesthetic agent was open drop ether. Sterile operative technique was observed. The hepatic arteries proper, along with the hepatic and gastroduodenal arteries, were isolated and a loop of heavy silk was placed loosely around them. A portacaval shunt was then done according to Freeman's (6) technique. The portal vein was ligated just as it entered the liver and at the same time, the loops around the arteries were ligated. Eight animals were premedicated with an antihistaminic (thenylpyramine HCl), 3 milligrams per kilogram 2 hours before ischemia, and half this dose repeated during the ischemia. Two other animals received hydrocortisone both intravenously and intramuscularly, 100 milligrams via each route.

One dog had the vessels ligated for 2 hours, 24 for 1 hour, 10 for 30 minutes, and 6 for 15 minutes. In 3 instances, dye excretion tests were done during the ischemia. The vessels were released by cutting the knots, and in all instances they seemed to regain their patency. In about half the cases, the vena cava was ligated above the shunt after the vessels were released. In 6 cases, the blood pressure readings were taken by the insertion of a cannula into a femoral artery. Twelve dogs received intravenous glucose during surgery; most of the others received this infusion 4 hours after the ischemia ended. The usual amount given was 600 cubic centimeters of 10 per cent dextrose in water. Penicillin, 600,000 units daily, was given postoperatively during the first 4 or 5 days. Liver function studies were carried out at varying periods after surgery. Most of the dogs had these studies done on the third and seventh days, and then weekly, until the values returned to normal. Postmortem examinations were done on the animals; those that appeared to survive indefinitely were sacrificed in from 2 to 6 months.

EXPERIMENTAL RESULTS

The dog whose afferent hepatic blood supply was ligated for 2 hours died 2 minutes after the vessels were released. Of the 24 dogs that were subjected to an hour of ischemia, only 1 survived, the others dying from 5 minutes to 20 hours after the vessels were released. The average survival time was 5.5 hours. The 1 surviving dog in this group tolerated the ischemia well and the liver function tests showed very little change. This dog was sacrificed 3 months later and the blood supply injected with latex rubber. Dissection revealed no abnormal vessels, and no anatomic reason could be found for its survival.

In 10 dogs, the hepatic blood supply was ligated for 30 minutes. Nine of these died, the survival times ranging from 4 hours to 40 days. The average was 6 days, and all of these animals showed progressive liver failure. The dye clearance remained poor, the phosphorus and phosphatase high, they lost weight, and the hematocrit levels fell. The 1

survivor in this group also developed liver disease, but appeared to be recovering when sacrificed 4½ months later. Only 2 of the 6 dogs whose vessels were ligated for 15 minutes died, and 1 of these had pneumonic consolidation. The survivors gave evidence of mild liver impairment for a few days and then returned to normal. Two to 5 months later these 4 dogs had an increased ability to excrete the injected rose bengal dye, being able to excrete the dye on an average of 38 per cent faster than in their control studies.

Blood pressure readings taken during the operative procedure showed an abrupt fall on release of the ligatures. The average drop in the 6 experiments was from 116 to 70 millimeters of mercury within 4 minutes. In 2 dogs, this pressure rose only slightly and the animals died 30 minutes later. In the other 4, the pressure rose almost to normal only to have a secondary drop in 3 to 5 hours.

Rose bengal dye clearances determined during the period of ischemia in 3 dogs were 10, 21, and 24, the normal being 90 to 110. No correlation could be noted between the degree of blanching, the dye excretion, and the survival time.

The dogs that survived the first half hour after the release of the vessels usually became conscious and were able to stand and walk. The pulse rate remained rapid and the mucosa pale. Coma came on either gradually, or suddenly, and was present about one-half hour before death. Two animals that had been subjected to 30 minutes of ischemia developed marked jaundice and died several days after surgery. One of these developed multiple bleeding peptic ulcers.

Blood glucose determinations in 12 animals showed a hyperglycemia 2 hours after the release of the vessels with a return to about normal 2 hours later. Eight determinations at the end of 24 hours showed only 1 that was abnormally low.

The administration of antihistaminics or hydrocortisone did not alter the survival time. The same was true of the postoperative glucose infusions, although the infusions given during surgery seemed to prevent the deaths that occurred a few minutes following the release of the vessels.

The surviving animals, as has been noted, gave evidence of liver disease by a lowered dye excretion, an increase in serum inorganic phosphorus, an increase in alkaline phosphatase, and in some cases, jaundice developed. The total proteins, albumin-globulin ratio, and serum potassium changed very little. The nonprotein nitrogen usually went up a little the first few days after surgery, but then dropped below normal. One animal developed a progressive rise to 165 milligrams per cent, but this was the only evidence of the elusive hepatorenal syndrome. Hematocrit readings were elevated for a few days, but then fell below normal.

The animals were autopsied shortly after death. In the dogs that survived a few days, the liver was yellowish brown and necrotic, while in those that survived only a few hours it was dark, engorged, and friable. The left lobes showed the more advanced changes. In several animals that died a few hours after surgery, there was quite a lot of serosanguineous fluid in the peritoneal cavity. Most of this was apparently from damage to the lymphatics in the hepatic pedicle during the dissection of the vessels. In a few instances, the blood failed to clot properly following ischemia, and the resulting blood loss killed the dogs.

DISCUSSION

While dogs can apparently survive ligation of the hepatic arteries or the portal vein, the ligation of both vessels, even for short periods of time, results in death. Even when these procedures are done 1 or 2 days apart, to allow for the formation of collateral circulation, about half the animals will die. The present study indicates that if the afferent hepatic circulation is interrupted for 30 minutes or longer, the dog will usually die. While the results are similar to the findings of Raffucci and Wangensteen, the studies are not comparable, in that they had simultaneously produced ischemia of the intestines, an organ that also has a very

TABLE I.—SUMMARY OF DOGS WITH TEMPORARY LIGATION OF THE AFFERENT BLOOD SUPPLY TO THE LIVER

Dog No.	*Time of ligation (min.)*	*Survival time*	*Vena cava ligated*	*Anti-hist.*	*Fluids during surgery*	*Comment*
451	120	2 min.	+			Dye clearance 10.0 during ischemia
474	60	5 min.	+			
8	60	10 min.	+	+		
477	70	30 min.	+			Blood pressure recorded
37	60	35 min.	+	+		Blood pressure recorded. Unsterile
78	60	1.5 hrs.				
498	60	2.1 hrs.	+			
223	60	2.5 hrs.			+	Hydrocortisone given
263	60	2.5 hrs.			+	Bloody fluid in abdomen on post
500	60	2.7 hrs.			+	Unsterile
224	60	3 hrs.			+	Hydrocortisone
278	60	4 hrs.			+	
245	60	4 hrs.			+	Blood pressure recorded
470	60	4 hrs.	+			Blood pressure recorded
82	60	5 hrs.				
81	60	5.3 hrs.			+	
76	60	5.5 hrs.				Dye clearance 24.0
266	60	5.7 hrs.			+	
251	60	7 hrs.			+	Blood pressure recorded
73	60	10 hrs.				Dye clearance 21.0
346	60	10.5 hrs.				Blood pressure recorded
15	60	13 hrs.	+	+	+	
27	60	17 hrs.		+		
499	60	20 hrs.	+	+	+	Terminal blood glucose 37.0 mgm. per cent
250	60	Indef.			+	Blood pressure taken. Sacrificed in 3 months
469	30	4 hrs.	+			
86	30	4 hrs.				
6	30	4 hrs.	+	+		Tonic convulsions terminally
83	30	16 hrs.				
446	30	40 hrs.	+			Icterus developed
468	30	56 hrs.	+			Very high phosphatase
459	30	3 days		+		Gas infection in liver
85	30	8 days				Ulcers and jaundice
403	30	40 days		+		Jaundice
87	30	Indef.				Recovered from liver disease
482	15	23 hrs.	+			
484	15	8 days	+			High phosphatase
480	15	Indef.	+			Sacrificed in 6 months
475	15	Indef.	+			Sacrificed in 5 months
491	15	Indef.	+			Re-explored in 2 months
488	15	Indef.	+			Dye clearance, 21.0. Re-explored

short tolerance for ischemia. The same is true in the studies of Bernhard.

Dye clearances during the ischemia indicated that there was an undetermined and variable amount of blood still reaching the liver. Variation in survival time could not be correlated with the degree of liver blanching or shrinking, the size or sex of the animal, or the use of antihistaminics.

In all 5 of the dogs that died within 30 minutes following an hour's ischemia, the vena cava was ligated above the shunt after the release of the vessels. The sudden blood pressure drop noted on the release of the vessels is probably due to the amount of blood needed to fill the ischemic liver. After the liver became congested, some pooling occurred in the portal circulation, and it is conceivable that this was further increased by ligating the vena cava above the shunt. None of the above 5 dogs received intravenous fluids during surgery.

The animals that died in from 2 to 20 hours were somewhat like the experimental shock dogs of Mylon and Winternitz (13). Of their 48 control dogs whose hind limbs were ischemic for 5 hours, only 1 survived, and the average survival time was 5.7 hours (14). In the present experiment, 24 dogs had an ischemic liver for 1 hour; only 1 survived, and the average survival time was 5.5 hours. Most of the dogs recovered from the

sudden blood pressure drop, but the pulse remained rapid (160 per minute) and the mucous membranes pale and cool. Shorr and associates reported the presence of a vasodepressor substance liberated by the liver during shock and that the healthy liver aerobically destroys this principle (1, 22). They later gave evidence to show that this substance was ferritin and that it produced circulatory failure by pooling blood in the portal system (12, 21). Other workers had some difficulty in reproducing these findings.

Hay has shown that experimental shock can be treated by improving the arterial blood flow to the liver. He improved the mortality rate by 900 per cent by creating arteriovenous shunts on the splenic vessels in dogs. Others have confirmed this observation. The possibility of the release of a histaminic-like substance contributing to the shock picture was considered, in that quite a lot of intracellular histamine has been recovered from the liver. However, antihistaminics, in the dosage used here, did not alter the survival time. Selkurt constricted the hepatic artery and portal vein for periods of from 1 to 2 hours, diverting the portal flow to the jugular vein with plastic tubing. He found the arterial blood pressure fell on release of the ligatures and that the portal pressure rose. He suggested that the hepatic resistance increased and the portal resistance was reduced. He also suggested the possibility of the release of substance into the circulatory system which can cause vasomotor collapse.

Some authors have found ACTH to be of value in treating shock produced by tourniquet, trauma to the cecum, and immersion. At the present time, this drug is being used in the study of dogs with experimental liver ischemia. Early results indicate that it may be of value in these animals, both in reduction of mortality rate and the degree of liver degeneration that follows the ischemia.

It was mentioned earlier that a subsequent increase in dye clearance above the normal range was noted a few weeks following the survival of a 15 minute period of liver ischemia. As controls, 4 dogs were subjected to reverse Eck fistulas and followed with liver function studies for periods up to 6 weeks. The dye clearances in these animals did not go above normal. This increased excretion could be due to the formation of additional collateral, or to regeneration of new hepatic cells, capable of removing the dye at a more rapid rate.

Those dogs which survived for more than 24 hours appeared to die of varying degrees of liver failure. Some acted like hepatectomized dogs, while others resembled chronic liver disease.

SUMMARY

The total temporary interruption of the afferent hepatic blood flow was studied in the adult dog. Of 24 dogs whose vessels were ligated for 1 hour, 23 died—the survival time varying from 5 minutes to 20 hours. Nine out of 10 whose vessels were ligated for 30 minutes died—the survival time being from 4 hours to 40 days. Only 2 of the 6 that had ligation for 15 minutes died. All of these animals received chemotherapy.

An attempt was made to correlate the blood pressure changes and certain other biochemical changes with the survival times in order to learn something of the nature of the cause of death in these animals. The immediate cause of death in dogs subjected to hepatic ischemia is accompanied by, or associated with, the development of a shock-like state. If this period is survived, manifestation of hepatic parenchymal disease develops.

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STUDIES ON GROWTH HORMONE

II. The Effect on the Nitrogen Metabolism of Severely Burned Patients

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THE USE OF GROWTH HORMONE[1] in humans as a means of inducing nitrogen storage is attractive to the surgeon, continuously confronted as he is by patients who could regain their health if only a means were found to heal their wounds and reverse their malnourishment by provision of an adequate intake of nitrogen (with calories and other nutrients), and by an endocrine (or possibly pharmacologic) mechanism for the reversal of the catabolic predominance which they exhibit. The provision of an adequate dietary intake cannot be discussed here, as it is a subject requiring extensive consideration in its own right. We shall confine ourselves to a consideration of posttraumatic metabolism and the possible means, if such exist, of shortening the duration of the catabolic phase with its resultant depletion of nitrogen.

Moore and others have shown in their careful investigations that in the characteristic metabolic response to surgery the period of nitrogen (and protein) loss varies from rather short periods of around 3 days up to months, depending upon the extent of the injury and its attendant and consequent events. In surgical procedures of a usual magnitude, such as herniorrhaphy, cholecystectomy, uncomplicated pulmonary resections, and so forth, the period of catabolic predominance is of rather short duration. This fact makes such clinical situations unsuitable to the evaluation of any agent for its effect on the synthesis of protein. For this purpose, one must have a circumstance in which the loss of body protein goes on over a period of some weeks. Under these conditions one can give the agent for definite periods of time, assessing its effect with control periods of varying lengths interposed between the experimental periods.

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[1]Hereafter referred to as GH.

METHODS

Such a procedure has been adopted in the present study of the effect of GH on the metabolic balances of 4 severely burned patients. In 3 of the 4 patients, the variability of the length of the control periods was a feature of the study.

Balance studies of nitrogen, potassium, magnesium, sodium, chloride, phosphorus, and calcium were done on patients A. W. and F. M., while the sodium, potassium, and nitrogen balances were determined on patients L. S. and C. A. This report will confine itself to the alterations observed in the nitrogen balance concomitant with the administration of GH, and the mineral balances will be discussed elsewhere (4). The details of collection, preparation, and analysis of the samples are given in a paper by Reiss and associates from this Unit. Table I is a summary of the study periods on each patient.

It has already been demonstrated by Reiss and associates that when the nitrogen balance is plotted against intake, good linear correlations can be demonstrated. We have, therefore, calculated the relationship between the nitrogen balance and the nitrogen intake in grams per square meter of

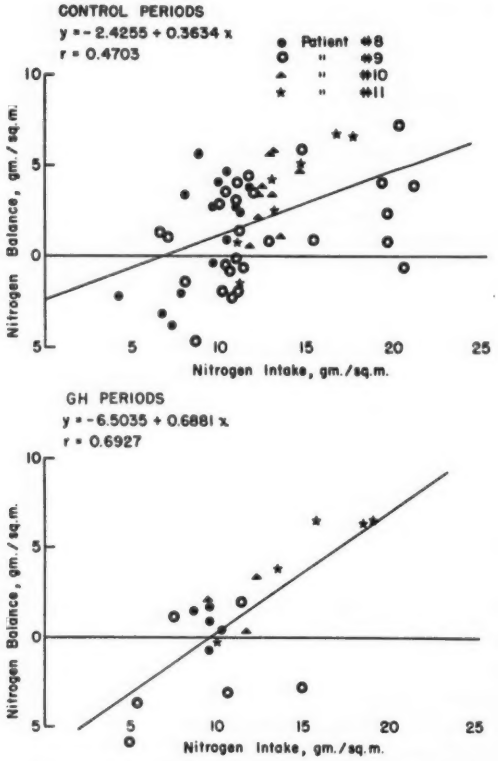

FIG. 1. "p" values for these correlation coefficients are both <.001.

body surface[2] for all patients. Use of surface area as a scale of reference "normalizes" this plot and makes it possible to pool all the patient data in this fashion. The characteristics of these two curves[3] are shown in Figure 1. The correlation coefficients are both significant; however, there is an appreciable deviation from exact linear correlation. This is probably due to the multiple sources of the data, and to the variable periods of convalescence from which they were collected.

The balances derived from the intake minus the urinary nitrogen have been plotted against the intake. The same technique has also been employed using the urea nitrogen rather than the total urinary nitrogen. It is believed that these plots afford a better index of nitrogen retention at various levels of nitrogen intake, since they avoid the variation of the highly changeable exudate losses. These plots (Figs. 2 and 3) are "normalized" by relating the variable to surface area as outlined before. Since the slopes of the lines are positive in both the control and GH periods, more nitrogen was retained as the intake increased. However, the retention per gram increment of intake was significantly greater ($p<.001$) during GH administration than in the control periods, as evidenced by the relative slopes of the lines.

We have also related the balance per gram of nitrogen intake to time, attempting thereby to account for both the intake and time variable simultaneously. This method of analysis is shown in Figures 4, 5, 6, and 7. For each fitted regression line, the y-intercept at zero time "b" (representing the time at which this study was begun), the slope of the lines, the X-intercept (or time at which the balance per gram of nitrogen intake was zero), and the correlation coefficient "r" have been determined. The values for all 4 patients are recorded in Table II.

TABLE I.—SUMMARY OF METABOLIC STUDY PERIODS

*Patient**	*No. of 5 day metabolic periods in study*	*Periods of GH given*
A.W. (Patient 8) 59 yrs.; 30 per cent total, 15 per cent 3°	21 Begun 18 days postburn	4, 6, 8, 12, 16
F.M. (Patient 9) 20 yrs.; 35 per cent granulating area	36 Begun 86 days postburn	6, 9, 12, 17, 24, 33
L.S. (Patient 10) 20 yrs.; healed 55 per cent 35 per cent 3°	12 Begun 124 days postburn	4, 9, 11 4, 9, 11
C.A. (Patient 11) 22 yrs.; 35 per cent granulating surface	12 Begun 47 days postburn	2, 4, 6, 8, 10

*The patient numbers refer to their assigned number in the metabolic unit, rather than to their sequence in this particular investigation.

[3]Calculated by the formula of Dubois and Dubois.

[4]These regression lines, as well as those to be discussed, have been fitted by the method of least squares. The line is expressed by the formula $y=b+mx$, where m = the slope of the line and b the y-intercept when $x=0$.

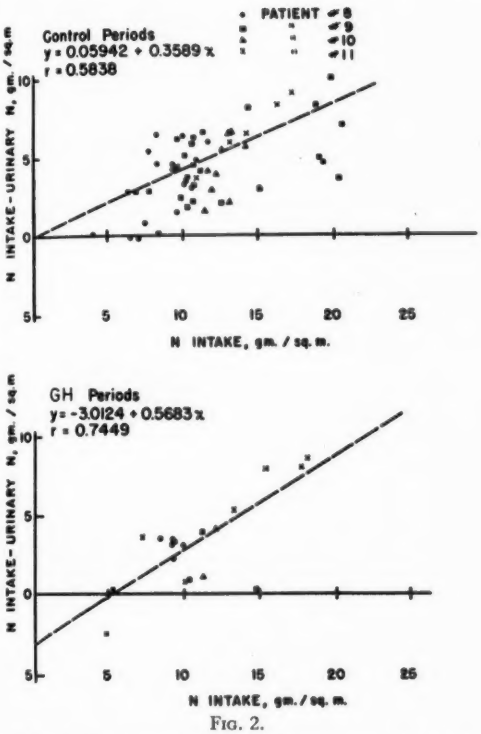
Control Periods
y = 0.05942 + 0.3589 x
r = 0.5838
PATIENT
N INTAKE - URINARY N, gm. / sq. m.
N INTAKE, gm. / sq. m.
GH Periods
y = -3.0124 + 0.5683 x
r = 0.7449
N INTAKE - URINARY N, gm. / sq. m.
N INTAKE, gm. / sq. m.

FIG. 2.

FIG. 2. Both correlation coefficients are highly significant (<< .001).

FIG. 3. Both "p" values <<.001.

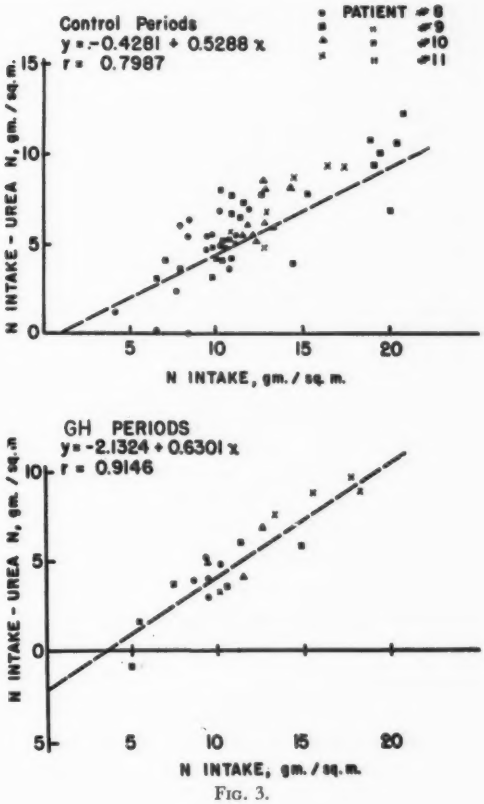
Control Periods
y = -0.4281 + 0.5288 x
r = 0.7987
PATIENT
N INTAKE - UREA N, gm. / sq. m.
N INTAKE, gm. / sq. m.
GH PERIODS
y = -2.1324 + 0.6301 x
r = 0.9146
N INTAKE - UREA N, gm. / sq. m.
N INTAKE, gm. / sq. m.

FIG. 3.

When the slopes in Table II are converted to percentages with the control slope at 100, an overall statistical comparison indicates a significantly ($p. < .001$) higher mean slope in the GH group. All correlation coefficients are highly significant ($p < .001$) except for the control on patient L. S. and the GH line on patient C. A. Their "p" values are ∽ .1 and <.02>.01. The latter value is also considered significant.

We have therefore seen that the use of all 4 of these correlation techniques have yielded results which are essentially the same. Although there appears to be a moderate variation within the individual plots which have been compared, the significantly greater slopes during the GH periods are striking.

DISCUSSION

Since the slopes of the GH groups are significantly greater than the controls in all our plots, one may conclude that growth hormone apparently caused a more rapid increase in the efficiency of nitrogen retention during the postburn course than was possible without it. It must be remembered, however, that the initial level of nitrogen storage efficiency is lower in the presence of GH (as evidenced by generally lower "b" values in all plots). Does the increased slope, therefore, only indicate that, as the patient convalesces, his nitrogen storage capacities approach the control level *despite* the growth hormone, the latter being incapable of reversing the powerful physiologic trend toward protein synthesis during anabolism? This possibility will be discussed.

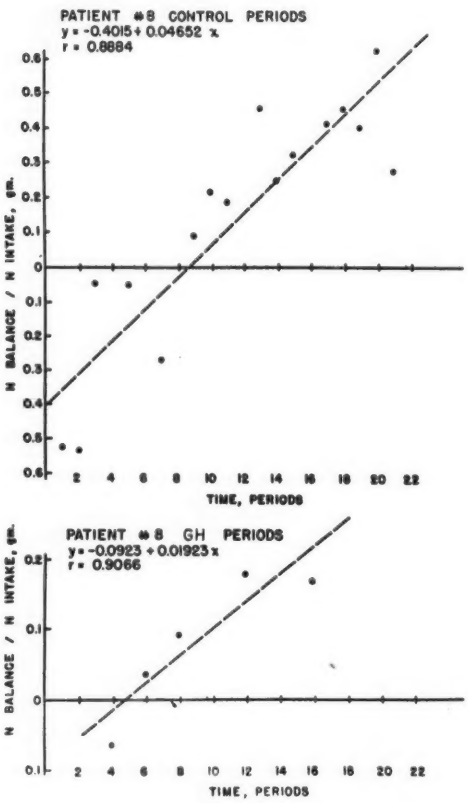
PATIENT #8 CONTROL PERIODS
y = -0.4015 + 0.04652 x
r = 0.8884
N BALANCE / N INTAKE, gm.
TIME, PERIODS
PATIENT #8 GH PERIODS
y = -0.0923 + 0.01923 x
r = 0.9066
N BALANCE / N INTAKE, gm.
TIME, PERIODS

FIG. 4.

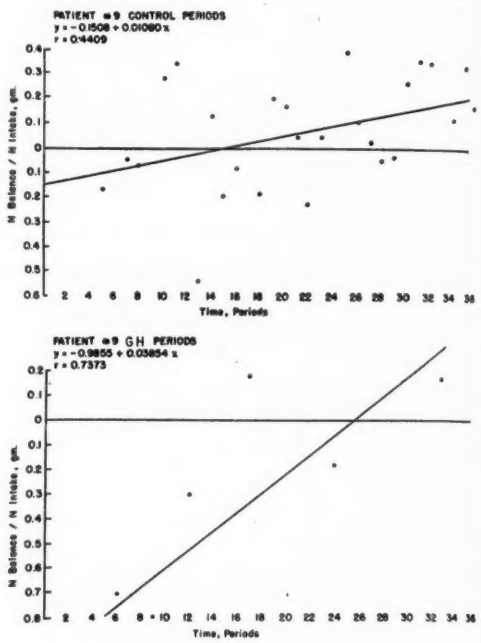
PATIENT #9 CONTROL PERIODS
y = -0.1508 + 0.01080 x
r = 0.4409
N Balance / N Intake, gm.
Time, Periods
PATIENT #9 GH PERIODS
y = -0.9855 + 0.03854 x
r = 0.7373
N Balance / N Intake, gm.
Time, Periods

FIG. 5.

FIG. 4. "p" values: controls—<.001; GH—<.01 >.001.

FIG. 5. "p" values: controls—<.05 >.02; GH—<.1 >.05.

The X intercepts in Figures 4, 5, 6, and 7, indicating the times at which the nitrogen balances reached zero, show that the controls were earlier 3 out of 4 times. It is considered that this has no necessary significance, because of the variations in time of beginning the studies, the length of the studies, and the pattern of administration of GH.

The correlation coefficients show that, in general, a highly satisfactory degree of linear correlation exists (see "p" values in legends). It is interesting to observe that the correlation coefficients shown in Table II were better 3 out of 4 times in the growth hormone series.[4] This, in combination with the significantly better GH "r" values in all 3 plots employing the nitrogen intake per square meter of body surface, may possibly be taken as evidence that the hormone was influencing the environment in a way so that the response to a given intake of nitrogen was more uniform.

For all patients the plots of the nitrogen balance versus the nitrogen intake per square meter of body surface show results which lead one to similar conclusions. For example, the "b" intercept is lower in the GH groups than in the controls, but the slope is significantly ($p<.001$) greater. One characteristic of these data which is particularly important can be seen on examination of the GH plots in Figures 1, 2, and 3—a considerable number of the points are above the level of zero balance. This indicates that we have not extrapolated from below a zero balance into the area of absolute nitrogen anabolism erroneously

[4]These particular correlation coefficients were significantly better twice and significantly less once.

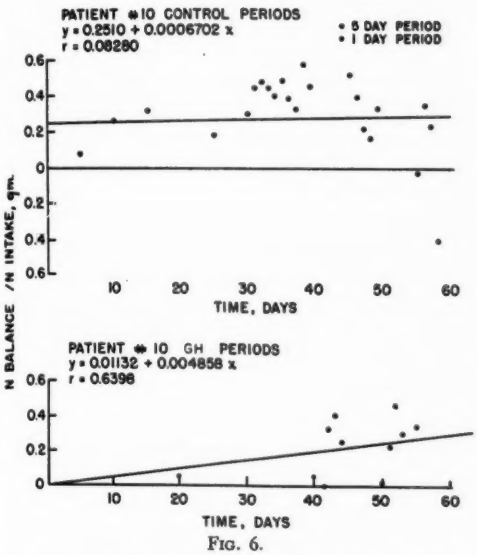
PATIENT #10 CONTROL PERIODS
y = 0.2510 + 0.0006702 x
r = 0.08280
• 5 DAY PERIOD
• 1 DAY PERIOD
N BALANCE / N INTAKE, gm.
TIME, DAYS
PATIENT #10 GH PERIODS
y = 0.01132 + 0.004858 x
r = 0.6396
TIME, DAYS

FIG. 6.

FIG. 6. "p" values: controls—>>.1; GH—<.01 >.001. In this plot, the open points are weighted, since they are for 5 day metabolic periods, whereas the solid ones represent 1 day.

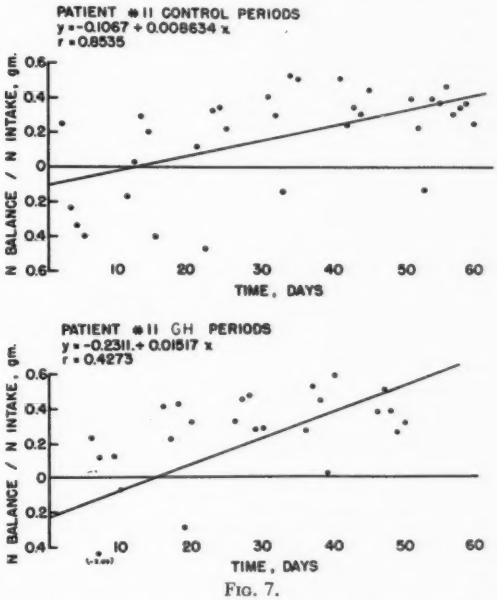
PATIENT #11 CONTROL PERIODS
y = -0.1067 + 0.008634 x
r = 0.8535
N BALANCE / N INTAKE, gm.
TIME, DAYS
PATIENT #11 GH PERIODS
y = -0.2311 + 0.01517 x
r = 0.4273
N BALANCE / N INTAKE, gm.
TIME, DAYS

FIG. 7.

FIG. 7. "p" values: controls—<.001; GH—<.02 >.01.

assuming a linear relationship which might not, in fact, exist. These data, therefore, indicate quite clearly that the fitted line of the GH data continues to rise at its own characteristic rate even after its level is above that of the control group. This is also true of the data when plotted as balance per gram of nitrogen intake versus time. Therefore, during spontaneous anabolism, growth hormone will apparently cause an increase in the existing anabolic tendency whenever it is possible to furnish the patient with a sufficient nitrogen intake as part of a balanced dietary regimen. The practicality of furnishing nitrogen intakes in the range of about 10 grams per square meter (the X intercept for the GH line in Fig. 1) in various clinical circumstances is a complex matter which cannot be dealt with in detail here. It is considered easily attainable[5] in almost all clinical situations during the latter portion of convalescence. Certainly, whether or not it is feasible in any particular circumstance will depend upon whether gastrointestinal surgery has been done, and how ill the patient may be due to clinical electrolytic, metabolic, or bacterial difficulties.

The plots relating the nitrogen retained to the intake (Figs. 2 and 3) are confirmatory. Indeed, these graphs gave the best correlation coefficients of any group, particularly when the urinary urea nitrogen was employed (Fig. 3).

These data permit certain tentative conclusions with regard to biologic mechanisms. Work from this laboratory on the incorporation of methionine-S^{35} into human plasma proteins while the subjects were or were not receiving GH (7), has shown that GH will cause a release of nonprotein S^{35} activity, followed shortly thereafter by increments in plasma protein specific activity. Urinary loss during these peaks has not been measured, but it seems relatively safe to sup-

[5]Levels of intake as high as 25 to 30 grams of nitrogen per square meter of body surface have been achieved in burned patients by this group by means of tube feedings (8).

TABLE II.—THE CHARACTERISTICS OF THE NITROGEN BALANCE PER GRAM OF INTAKE VERSUS TIME CURVE

	GH	*Control*
"b" (nitrogen balance per gram of nitrogen intake at start of study)		
A.W. (8)	−0. 0923	−0.4015
F.M. (9)	−0.9855	−0.1508
L.S. (10)	+0.0113	+0.2510
C.A. (11)	+0.2311	−0.1067
Slopes of regression lines		
A.W. (8)	+0.01923	+0.04650
F.M. (9)	+0.03854	+0.01080
L.S. (10)	+0.00485	+0.00067
C.A. (11)	+0 01517	+0.00863
X intercept (period of zero balance)		
A.W. (8)	+ 4.79	+ 8.63
F.M. (9)	+25.60	+ 13.96
L.S. (10)	− 0.23	−374.52
C.A. (11)	+15.23	+ 12.63
"r" (correlation coefficients)		
A.W. (8)	0.9066	0.0886
F.M. (9)	0.7373	0.4409
L.S. (10)	0.6398	0.0828*
C.A. (11)	0.4273	0.8535

*The essential flatness of this line makes this particular correlation coefficient a poor reflection of the grouping of the points about the linear fit (since deviations from the line will be relatively greater in reference to the magnitude of the linear progression.

pose that there is an increased renal loss of activity at that time. Therefore, in the normal and burned humans upon whom these studies were done, GH apparently caused a release into the plasma of amino acids, some of which were used for plasma (and presumably tissue) protein synthesis, and some of which were excreted. These data agree with the experiments reported here, since one must postulate an increased excretion of amino acids and low molecular weight peptides under the influence of GH in order to understand the lower efficiency of nitrogen metabolism when GH is administered during the catabolic reaction to surgery or trauma.

These observations are reinforced by the evidence obtained in liver perfusion studies (5) indicating that GH will cause a diminution in the polypeptide fraction and a relative increase in the amino acid concentrations.

Why then is the efficiency of nitrogen storage altered in the presence of GH (as already indicated)? This matter is insufficiently investigated to permit more than speculation at this time. It is possible that a GH enhancement of enzyme adaptation to increasing substrates (in this case, to the increasing amounts of "free" amino acids) may be important, although it is difficult to understand how this could account alone for the decreased efficiency on low intakes. Theoretically, it is possible that it might be due to the presence of maximal renal clearance rates for certain amino acids or other key synthetic materials which are exceeded in the presence of a high intake whether or not the patient was on GH. This would permit the patient to conserve these materials in a progressively more efficient way as the intake increased, taking advantage of the increased relative amounts of nitrogen available in the form of amino acids to build more tissue protein.

Whatever the ultimate explanation of these observations, it appears that the administration of GH is a matter calling for some nicety of clinical judgment. One infers that it should be withheld until the patient has begun to accept relatively large intakes (at least 10 to 12 grams of nitrogen per square meter of body surface). When this is achieved spontaneously, or by successful tube feeding, GH may, in the presence of a definite physiologic anabolic state, speed the restoration of depleted tissue protein and hasten clinical recovery. It remains to be seen whether a large intake of nitrogen, as part of a balanced regimen, will make possible the same beneficial effect of GH as has been demonstrated to occur during anabolism. Superficially, the plots of nitrogen balance versus nitrogen intake would appear to indicate that this is the case; but the graphs relating the nitrogen balance per gram of intake to time show that the patient's physiologic status has a definite effect on his nitrogen retentive abilities. In these plots, the early points (during catabolism) in the growth hormone periods were uniformly below those of the control periods during catabolism. This then presumably means that the slopes of the balance versus intake plots have the additional variable of the changing physiologic status in them, and that GH is actually detrimental in the catabolic state despite its apparent bene-

fits in anabolism. This problem is under more precise evaluation at present (3).

SUMMARY

1. The effect of growth hormone upon the metabolic balances of 4 severely burned patients was determined.

2. Definite effects on the nitrogen balances were discernible when the control and growth hormone data for each patient were graphed separately as nitrogen balance per gram of intake versus time, and when all patients were divided into the growth hormone and control groups respectively and plotted as nitrogen balance per square meter of body surface versus nitrogen intake per square meter of body surface. Equally definite results were obtained when estimates of the nitrogen retained per square meter body surface (calculated by subtracting the total urinary nitrogen or the urinary urea nitrogen from the intake) were plotted against intake per square meter of body surface.

3. These analyses indicate that growth hormone will bring about an increase in the retention of nitrogen during anabolism, and that during catabolism its effect is a *deleterious* one regardless of the intake of nitrogen provided. This infers that growth hormone requires the presence of additional endocrine factors (and possibly the absence of others) in order to cause a more effective nitrogen anabolism.

4. Possible physiologic mechanisms are discussed.

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CELLULAR CHANGES DURING SURGICAL STRESS

I. Morphologic Alterations in Hepatic Cells

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THE INFLUENCE OF SURGICAL STRESS on physiologic and metabolic processes of the organism is well known. The changes in the chemical composition of the body fluids, in electrolytes, in carbohydrate and protein metabolism, and hormonal activity of the adrenal and pituitary glands observed in the postoperative period are a few examples which serve to emphasize the alterations following surgical stress. While there can be no doubt that such alterations must be an expression of profound chemical *cellular* changes in the organs, very little work has been done in the past in a direct study on cells themselves. While this may seem surprising at first, it can probably be explained in part by the lack of suitable methods which would allow such chemical studies on a cellular level. However, this type of investigation is now made possible by the recent development of microspectrophotometric techniques as described by Pollister and Leuchtenberger. These methods permit a quantitative chemical analysis of single cells in situ directly under the microscope.

In the past year and a half, we have been engaged in an extensive investigation of the possible morphologic and chemical changes which may occur in cells or cell parts (such as nucleus, nucleolus, and cytoplasm) after surgical stress. The following report is concerned only with one of the aspects: the morphologic changes observed in the hepatic cells of dogs 3 to 96 hours after operations of varying degrees of severity involving other organs.

From the Departments of Surgery and Pathology, Western Reserve University School of Medicine and University Hospitals of Cleveland.

This work was supported by a Grant No. RG 4268 from the National Institutes of Health, U. S. Public Health Service.

METHODS

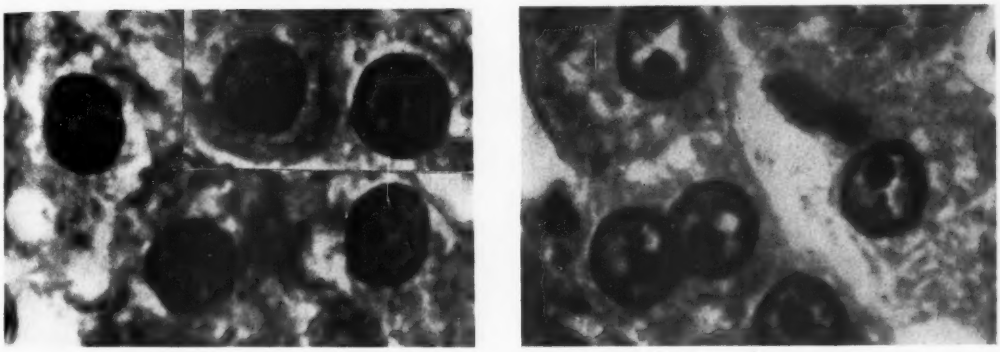
All animals, a total of 18, in this study were healthy mongrel dogs. They were maintained on a standard kennel ration during a period of preoperative preparation ranging from 6 to 10 days. All animals prior to surgery were gaining weight and were in apparent good health. Intravenous nembutal, 0.5 cubic centimeter per kilogram of body weight, was the anesthetic used in all experiments. In all of the animals operated upon liver biopsy was obtained immediately upon entering the peritoneal cavity, a second biopsy was obtained prior to closing the abdominal wall, and a third biopsy was made at the time the animal was sacrificed. The biopsy specimens were taken from widely separated areas of the liver and handled identically following removal. The tissues were placed immediately in Lavdowsky's solution, embedded in paraffin by the usual procedures, and sectioned at 6 microns. The preoperative and postoperative liver biopsy specimens of any individual animal were mounted on the same slide and stained with hematoxylin and eosin. The slides were examined under oil immersion.

Four different groups of animals comprise this study.

Group I (3 animals). Received only intravenous nembutal anesthesia. Sacrificed at either 6 hours or 3 days following anesthetization.

Group II (4 animals). Underwent exploratory laparotomy. Sacrificed 6 hours following surgery.

Group III (7 animals). Subjected to subtotal gastrectomy. Five animals sacrificed 6 hours following surgery, 1 animal 3 hours



a b

FIG. 1. Photomicrograph of liver nuclei stained with hematoxylin and eosin from animal undergoing exploratory laparotomy. a, Nuclei as they appeared at the beginning of the procedure. b, Nuclei 3 hours following completion of surgery showing coalescence of nuclear chromatin, areas of rarefaction within the nucleus, enlargement of the nucleoli, and an increase in the nucleolar associated chromatin.

following surgery, and 1 animal 72 hours following surgery.

Group IV (4 animals). Cholecystectomy performed. Two animals sacrificed on third postoperative day, 1 animal 24 hours after surgery, and 1 on fourth postoperative day.

All of the animals in these groups had uncomplicated postoperative courses.

RESULTS

When liver sections of these dogs were examined microscopically, marked differences in cell morphology between the preoperative and postoperative livers were readily apparent. The chromatin appeared finely granular and evenly distributed throughout the nuclei in livers from the preoperative dogs. In the postoperative dogs, the chromatin in the nuclei was coarse, coalescent, and irregularly distributed, and there were large rarified areas within the nuclei. The nucleoli of the hepatic cells prior to surgery were deeply stained and presented smooth discrete margins. This was in marked contrast to the nucleoli in the cells from the postoperative livers, which, while equally well stained, were larger, showed irregularly distorted borders and an abundance of "heterochromatin" or nucleolar associated chromatin as demonstrated in the accompanying photomicrograph (Fig. 1).

The changes in the nuclear chromatin and nucleoli were most extensive in the hepatic cells from livers of the animals sacrificed 3 to 6 hours following surgery, while hepatic cells from the animals sacrificed 3 to 4 days after surgery manifested no appreciable changes in cell morphology when compared with the preoperative specimens. On the other hand, the severity of the surgical procedure did not seem to play a significant role since the cytologic changes were observed after exploratory laparotomy as well as following subtotal gastric resection.

Hepatic cells from animals receiving only intravenous nembutal anesthesia did not differ significantly from the preoperative control specimens. In both groups, the majority of the liver cells had a normal appearance and only occasionally were liver cells encountered which resembled those of the postoperative cases.

In Table I an attempt is made to represent the frequency and degree to which the previously described cellular alterations were noted in the hepatic cells of experimental animals.

DISCUSSION

Interpretation of these cellular changes is hardly feasible at this time. However, there are several points worthy of discussion.

TABLE I

Dog No.	*Type of stress*	*Time of sacrifice after stress, hrs.*	*Change in nuclear chromatin and nucleoli of liver cells*
1726	Anesthetized	6	0
1660	Anesthetized	6	0
1722	Anesthetized	72	0
1831	Laparotomy	6	+++
1832	Laparotomy	6	++++
1817	Laparotomy	6	+++
1818	Laparotomy	6	++
1688	Cholecystectomy	24	+
1531	Cholecystectomy	72	++
1565	Cholecystectomy	72	+
1599	Cholecystectomy	96	0
1786	Gastrectomy	3	++++
1725	Gastrectomy	6	++
1769	Gastrectomy	6	++++
1785	Gastrectomy	6	++++
1797	Gastrectomy	6	++++
1798	Gastrectomy	6	++++
1710	Gastrectomy	72	+

First is the rapidity with which these cellular changes occur following surgery. This finding is of particular interest in light of the fact that the liver itself was only mildly traumatized during the procedure. As a matter of fact, the liver specimen removed after surgery came from liver lobes different from the one from which the preoperative liver biopsy specimen was taken. It looks as if the liver cell changes may possibly be a result of trauma in tissues distant from the liver itself. That these changes are not caused by altered hemodynamics or anesthesia, as might be expected, is supported by the fact that animals subjected to simple laparotomy where blood loss was negligible did show the changes. On the other hand, animals receiving only anesthesia did not show hepatic cellular changes.

A second noteworthy aspect is the resemblance of the cytologic appearance in the liver cells from dogs operated upon to normal liver cells which are actively engaged in protein synthesis. A detailed description of these changes in normal cells has been made by both Caspersson and Lagerstedt. The possibility that these alterations in the postoperative liver cells are a reflection of the increased demand for protein synthesis and tissue repair is an intriguing idea. Additional evidence in support of this hypothesis is provided by recent observations in this laboratory. We have found that there was an increased tyrosine concentration in the cytoplasm and to a lesser extent in the nuclei of liver cells from postoperative dogs. A detailed report of these findings will appear elsewhere.

SUMMARY

1. Cytologic alteration characterized by condensation of nuclear chromatin and increased nucleolar associated chromatin were noted in the hepatic cells following laparotomy, cholecystectomy, and gastrectomy.

2. These changes in the liver cells were observed as early as 3 hours after surgery and resemble cytologic changes normally observed in protein synthesis.

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THE PATHOGENESIS OF HYPERTROPHIC STENOSIS OF THE PYLORUS IN THE NEWBORN AND THE ADULT

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HYPERTROPHIC STENOSIS of the pylorus in the newborn and achalasia of the pylorus in the adult are conditions which have been known for many years by different names depending upon the conception of different authors. However, since the description of the first cases, the conditions in adults and newborns were thought to be the same—that both were congenital and that they differed only in the age at which the symptoms appeared. The predominant theory concerning the pathogenesis was based upon the presence of hypertrophy of the pyloric muscles.

Since the classical description by Hirschsprung in 1888 of hypertrophic stenosis of the pylorus in the newborn, many reports have appeared in the medical literature, and the problem has been exhaustively studied. The condition was always easily recognized in children because one of its features, hypertrophy of the muscles of the pyloric antrum, was found in the majority of cases, and there was no possibility of confusing it with other conditions. Even though these studies did not clarify the problems of etiology and pathogenesis they solved those of diagnosis and treatment.

On the other hand, the medical literature on achalasia of the pylorus in the adult is scant and confusing, possibly because the condition is rare in adults, and the clinical and pathologic pictures are not as clear-cut as in infants. For this reason, since its first description in adults by Cruveilhier in 1885, it has been confused with other similar conditions and has not been well defined. The majority of investigators who studied the condition considered it the manifestation, in adulthood, of a congenital disease. Thus, they looked for the same pathologic features found in the newborn and tried to identify only hypertrophy of the pyloric antrum. However, in adults, hypertrophy of the muscles of the pyloric antrum may have various causes, such as hypertrophy of the mucous lining, narrowing of the lumen by scar tissue, myomas, and fibromas. This fact resulted in further confusion since often no study was made of the microscopic pathology to identify lesions of the plexuses of the gastric wall; only the hypertrophy of the pyloric antrum was noted, and often tentatively described as a new disease. Only after the work of Corrêa Netto, who made a detailed clinical study, was the condition clearly defined and distinguished from similar entities or was achalasia of the pylorus identified with achalasia of other sphincters of the digestive tract. Raia (21) confirmed these data and presented more cases describing the lesions of the myenteric plexuses in the pylorus. These lesions were similar to those found in the esophagus and the colon in cases of acquired megaesophagus and megacolon.

Based on these studies, an attempt was made to correlate the pathogenesis of hypertrophic stenosis in the newborn and of achalasia of the pylorus in the adult. Etzel advanced the theory that hypertrophic stenosis of the pylorus in the newborn was caused by inadequate development of the

FIG. 1. Longitudinal section of the pyloric antrum of a newborn with hypertrophic stenosis of the pylorus. The pylorus is not visible as a separate muscular bundle as demonstrated by Cameron. ×13.

myenteric plexuses of the pylorus while in the adult the condition was caused by lesions of these plexuses. This fact was demonstrated in relation to the megacolon. It was shown that congenital megacolon was caused by agenesis of the myenteric plexuses, as reported by Swenson and associates in 1949, Bodian and associates, and Ehrenpreis in 1951, while acquired megacolon was secondary to lesions of the myenteric plexuses according to Amorim and Corrêa Netto, Etzel, Vasconcellos and Botelho, and Raia.

The same conditions were not observed when hypertrophic stenosis of the pylorus was studied in the newborn and in the adult. In this article we wish to demonstrate that the pathogenesis is the same in the newborn and in the adult—namely, alterations of the myenteric plexuses of the pylorus. However, these changes are mild and reversible in infants and marked and irreversible in adults.

Concurrence of achalasia of the pylorus and of other sphincters of the digestive tract has been noted in infants and adults. In 1931, Pritchard and Hillier observed hypertrophy of the muscles of the inferior portion of the esophagus, pylorus, and ileocecal sphincter at autopsy of a 3 month old baby. In 1949, Chiabi reported that Guthrie had noted marked muscular hypertrophy of the pylorus, duodenum, jejunum, and esophagus at autopsy of an 11 year old girl. Ehlers described a case of achalasia of the pylorus and megaesophagus in an adult. Chiari observed the same concurrence of lesions in an adult patient. These authors did not make a careful pathologic study and did not try to correlate, or to identify their various findings.

The investigations made on megaesophagus and megacolon led to the study of the pathologic anatomy of achalasia of the pylorus. Hurst and Rake, studying achalasia of the cardia, referred to the occasional concurrence of dilatation of the stomach and megaesophagus but had not observed an instance of this condition. Corrêa Netto demonstrated clinically that in adults the achalasia of the pylorus and the achalasia of the cardia and the sphincters of the colon were identical. After the first description of the condition in both the newborn and the adult, an attempt was made to identify it on the basis of the hypertrophy of the pyloric muscles found in both so that only the cases of hypertrophy of the pyloric antrum were described as achalasia of the pylorus.

German and Swedish authors have had a different conception of the condition in the newborn; they included the cases of pylorospasm with no definite hypertrophy of the muscles of the antrum. Lehmann explained these cases as noncompensated achalasia, which we believe to be correct, and in accordance with observations made in adults since marked hypertrophy of the pyloric muscles is not frequent in adults. These findings indicated to us that the condition might occur without marked muscular hypertrophy. In the newborn, the cases described as pylorospasm are benign forms of the condition in which the histopathologic changes of the myenteric plexuses, to be described, are minimal and curable. This theory seems the most reasonable since the cause of the so-called spasm has not as yet been found.

In the newborn, hypertrophy of the muscles of the pyloric antrum is frequent, while

FIG. 2.

FIG. 3.

FIG. 2. Longitudinal section of the pylorus of an adult with achalasia of the pylorus. The muscles of the antrum are not greatly hypertrophic. ×13.

FIG. 3. Longitudinal section of the pylorus of an adult with achalasia of the pylorus. There is marked hypertrophy of the muscles. ×3.

in the adult it is rare. Cameron studied the specimens collected by Thomson from newborns and found that the pylorus was not thickened but that there was great enlargement of the pyloric antrum. From our study of microscopic sections through the muscles of the pyloric antrum, the same conclusion was not reached. In the newborn, the whole antrum was hypertrophic. The hypertrophy diminished beyond the pylorus, and it was not seen as a separate muscle bundle.

While hypertrophy is most prevalent in children and was found in all cases that we studied, it is rare in adults, although it may exist (Fig. 3). Corrêa Netto observed it during an operation, and in Figure 2, in a section taken from an adult, a discrete degree of hypertrophy is shown. When hypertrophy is present it occurs in the circular layer. The muscularis mucosae is also hypertrophic, a fact which had already been observed by Cameron. The mucosa is generally normal in appearance. These findings are similar to those seen in the colon and esophagus in cases of megaesophagus and megacolon.

Stenosis cannot be seen. In the adult, the pylorus is easily penetrated which can be verified at operation by the introduction of the finger through the sphincter. In the infant, the peritoneum covering the pyloric antrum is not very elastic, and marked hypertrophy of the muscles, which grow inward toward the lumen, suddenly transforms the antrum into a rigid tube and also causes the pyloric muscles to protrude into the duodenal lumen. Nevertheless, autopsy shows that there is no pyloric stenosis, as the pylorus is penetrable by a stylet.

The stomach is generally enlarged, sometimes markedly so, as can be clearly seen in the newborn at operation or by x-ray examination. In the newborn, definite peristaltic waves may be seen, while not so in the adult whose muscles have already lost their tonus.

Histologically, the lesions seen in the myenteric plexuses of the pylorus in cases of hypertrophic pyloric stenosis can be correlated with those in the esophagus, colon, and heart in patients with megaesophagus and megacolon. In 1930, Herbst was the first to study the intramural plexuses of 2 infants with hypertrophic stenosis of the pylorus during autopsy and observed the following: (1) degeneration of the cells and axis-cylinders of the plexuses of Auerbach (some plexuses were completely destroyed); (2) round cell infiltration in many ganglions and nerves; (3) apparent increase

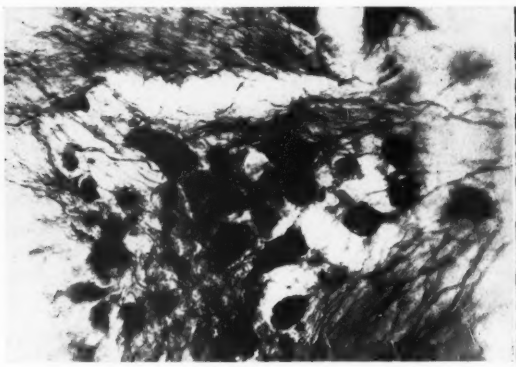

FIG. 4.

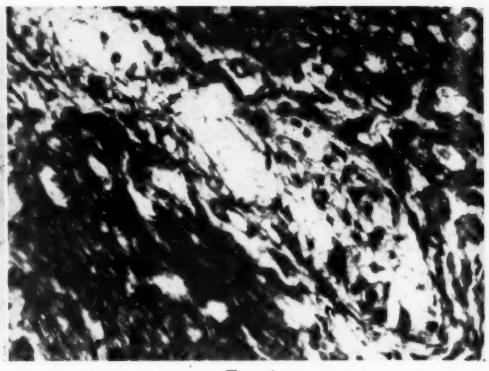

FIG. 5.

FIG. 4. Section of the myenteric plexus in an adult. Type I cells are impregnated; there is a great number of intrinsic fibers—the fine fibers—and some extrinsic fibers—thicker and varicose. Bielchowski and Gros, ×340.

FIG. 5. Ganglion of myenteric plexus of newborn patient with hypertrophic stenosis of the pylorus. There are vacuolized cells, with blurred limits, without nuclear lesions. Bielchowski and Gros, ×340.

of the nerve tissue, over the physiologic limit in isolated zones.

In 1953, Belding and Kernohan made a microscopic study of the stomach of 9 children and 5 adults with hypertrophic stenosis of the pylorus and observed the following: (1) decrease in the number of cells of the myenteric plexuses in the antrum; (2) degenerative alterations in the majority of cells of the intramural plexuses of the pyloric region, while those of the duodenum and the suprapyloric region were normal. Corrêa Netto mentioned the histopathology described by Etzel in 1 case of achalasia of the pylorus.

In a microscopic study of hypertrophic stenosis of the pylorus in the newborn, Raia (22) found lesions in the plexuses of Meissner and Auerbach in this region, varying degrees of degeneration of the neurons, and granulous fragmentation of the axis cylinders of the nerve fibers. In 1944, Raia, studying achalasia of the pylorus in the adult, described lesions of varying degree in the nerve cells and fibers of the myenteric plexuses of the pyloric region which could lead to complete destruction of the nerve elements that were replaced by connective cells.

In the present study, we have studied these lesions in a greater number of cases of achalasia of the pylorus in newborns, adolescents, and adults and have compared our findings.

MATERIAL AND METHODS

In order to study the lesions of the myenteric plexuses of the pyloric region in newborns, adolescents, and adults, it was necessary to have a thorough knowledge of the normal histology of the intramural plexuses of the pylorus. Therefore, before examining specimens from patients with achalasia of the pylorus, we studied the plexuses of the region in 2 newborns and in 2 adults without lesions of the stomach. The 17 specimens examined have been divided in three groups:

Group I. Two specimens from normal newborns and 2 from normal adults were studied to establish a basis of comparison with the cases suspected of plexal nerve lesions. This material was obtained at autopsy from cases in which there had been no condition harmful to the nerve structure of the pylorus.

Group II. Five specimens were obtained from newborns with achalasia of the pylorus.

Group III. Eight specimens were taken from adults with achalasia of the pylorus.

TECHNIQUE

The specimens examined were fixed in 10 per cent formalin, and the sections were ob-

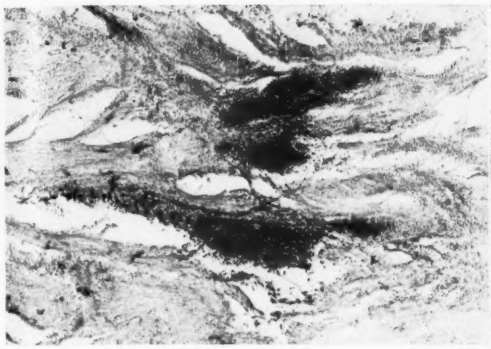

FIG. 6.

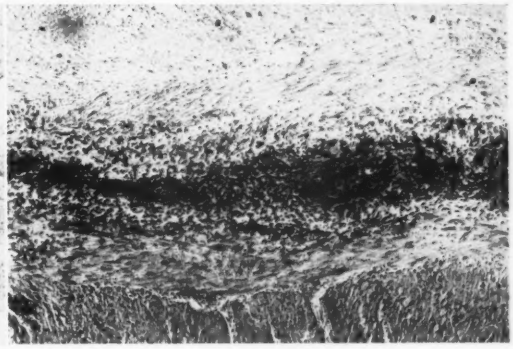

FIG. 7.

FIG. 6. General picture of the myenteric plexus of the pyloric antrum of an adult patient with achalasia of the pylorus. Terminal stage of lesion is demonstrated by concentric fibroblastic proliferation. Bielchowski and Gros, ×66.

FIG. 7. A greater magnification of Figure 6. ×80.

tained either by longitudinal section, following the greater axis of the pyloric canal, perpendicular to the serosa, or by parallel section, tangent to the serosa, in order to show a greater number of nerve elements. The sections were stained by different methods: hematoxylin and eosin, van Gieson, Ungewiter for nerve fibers, and Bielchowski and Gros.

MICROSCOPIC STUDY

Group I, the normal cases, was studied first. The neurons and the plexuses of intrinsic and extrinsic fibers were clearly visible in these sections. We were able to confirm the data of Stöhr, Irwin, and Kollossow, and Sabussow, with reference to the dimensions of the ganglions, their abundance of neurons, and also the existence of type I and type II cells of Dogiel. The fibrillar pattern of the cellular elements of the fibers was also well impregnated. In some sections, the intrinsic fibers could be followed to the point where they ended in the muscular fibers. The thick and various extrinsic fibers could also be seen. In some cases, it was possible to observe their ending in pericellular baskets.

In the newborn (group II), we also found a dense network of ganglions with well stained neurons. The histologic study of the wall of the antrum showed that the myenteric plexuses had a different pattern—the ganglions were present not only in the fibrous tissue which separated the internal circular layer from the external longitudinal layer but also between the muscle bundles of the wall. This arrangement probably depended on the difference in organization of the muscle bundles of the gastric wall. There was no decrease in the number of neurons which formed the ganglions in comparison with the normal subject. However, many ganglions were swollen, and there was clear separation of the neurons forming them. These showed two types of changes: (a) some cells were swollen with clear cytoplasm, had marked limits, and showed no nuclear changes; (b) others showed marked protoplasmatic vacuolization and blurred limits. The nucleoli also showed no signs of degeneration. These two types of changes were frequently found in the same nerve ganglions. These ganglions, thus altered, were irregularly distributed in the surface of the antrum but fewer near the pylorus. At the pyloric sphincter, the majority of the neurons were of normal appearance.

Examination of the sections in group III, obtained from adolescents and adults with achalasia of the pylorus, showed changes far more advanced. Even at low magnification, marked cellular infiltration of the ganglions

was noted (Fig. 6). As illustrated in Figure 7, more pronounced lesions of the scarring type with sclerosis of the old ganglionic mass were present in the plexuses. The nerve structures were totally destroyed and replaced by connective hyperplasia. Only traces of the neurons were present, represented by argentophil residues. Proliferation nests which had been formed were substituted by new growth tissue and by the regional part of the peripheral connective envelope. Nevertheless, the limits of the old ganglionic mass were still visible. A proliferation of fusiform elements was distributed in all directions noticeable by the elliptic form of their nuclei. In some places the old neuron had been replaced by a residual nodule (Fig. 8). In the periphery of these ganglionic remnants isolated fibers or bundles of fibers were seen to enter and leave, spared because they were preganglionic or postganglionic exogenous fibers. This description corresponded to the picture of the most advanced process, in which complete destruction of the nerve elements and replacement by scar tissue had occurred. There are, however, different stages of the lesions, as well as different degrees of degeneration of the cells—from the mere blurring of their limits to disappearance and replacement by a residual node.

One fact must be kept in mind; that proliferation of the connective tissue was seen only at the nervous plexuses. There was none or little infiltration of the interstitial tissue of the muscular layer which demonstrated that the etiologic agent reached the nerve ganglions specifically and that the degeneration was not caused by inflammatory lesions of the gastric walls. The bundles of fibers away from the plexus trunks were largely totally degenerated. Impregnation of the axis-cylinder was no longer possible, which demonstrated the advanced degree of degeneration of the neuron. There was only a grayish shadow marking the site of the fibers, on the nuclei of the proliferation satellite cells (Fig. 9).

Even in this picture of total destruction of the intrinsic fibers, there were well impregnated fibers, in contrast to the gray bundles of degenerated intrinsic fibers. These normal fibers, thus impregnated, showed typical patterns; they were varicose, and their borders were irregular with lateral spines due to the corpuscles of Golgi; their nerve elements were not affected by the degenerative process which attacked only the intramural neurons. The final lesion of the intrinsic axis-cylinder was always preceded by its granulous fragmentation. It was sometimes visible in the plexus of the nerve ganglions in the early processes. When the different observations were compared, the same degree of degeneration and stage of development of the condition were not found in different sections from the same patient; the degree of degeneration noted was not the same in all plexuses. Thus, side by side with plexuses which were totally destroyed were not only others in different stages of degeneration but even normal plexuses.

When the histopathologic changes of the myenteric plexuses in children and adults were compared, the conclusion was reached that in the newborn they are very slight. In no case was there the same degree of degeneration seen in the child as in the adult. In the former, the changes were reversible while in the latter the neurons were so degenerated that there was no possibility of regeneration. This is a very important fact as it indicates that although the condition shows the same pathologic nature in newborns and in adults, that is, changes in the myenteric plexuses of the pyloric antrum, the condition can heal spontaneously in children but not in adults.

This factor gives us the key for interpreting the results obtained by different forms of treatment. The fact that in children cure can be attained spontaneously or by medical treatment alone, as has been noted in the available medical literature, leads us to believe that the alterations in the newborn are reversible, at least in part. In corroboration of this theory the pathologic study made by Wollstein and Miller indicated that some months after surgical treatment by the Fredet-Ramstedt method there was a scar in the

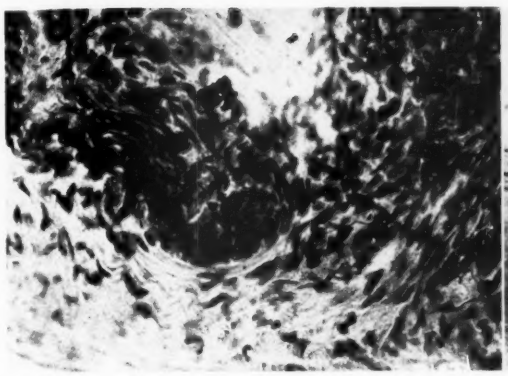

FIG. 8.

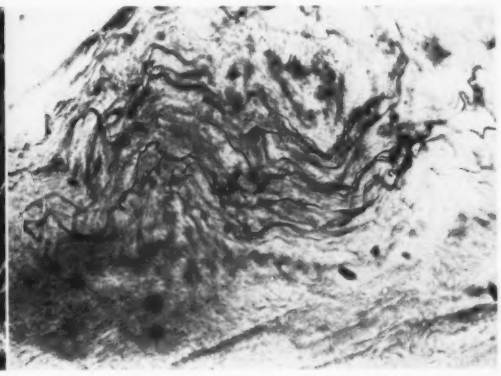

FIG. 9.

FIG. 8. Residual node of Nageotte. Bielchowski and Gros, ×335.
FIG. 9. Absence of intrinsic fibers in a plexus segment; only the thick and varicose fibers are seen (extrinsic fibers). ×335.

pyloric antrum at the site of the first incision which re-established the continuity of the muscular fibers. This did not bring about recurrence of the symptoms, a fact which can only be explained by the reversibility of the plexus alterations. This reversibility is not complete, as proved by the work of Belding and Kernohan. In a study of the myenteric plexuses of patients who died several years after the operation as a result of intercurrent disease, they observed degenerated neurons and normal neurons in the antrum in sufficient amount to re-establish the peristaltic synchronism.

The methods of treatment used in children did no more than permit the patient to maintain a metabolic balance during the period in which the natural reversion of the histopathologic alterations took place. This period varied with the extent and degree of the changes. When the alterations were not marked the patient was spontaneously cured; others needed intensive medical treatment; while still others had to be treated surgically in order to destroy the obstacle at the pylorus and attain a balanced metabolism, while reversion of the alterations, which in these cases was a slow process, took place. The best surgical treatment is the Fredet-Ramstedt operation which presents a very low mortality. In adults the lesions are irreversible, thus the treatment should always be surgical by the Finney pyloroplasty.

In view of the histopathologic findings, we believe that the pathogenesis of the condition can be explained on the basis of Hurst's theory of achalasia. Lesions of the myenteric plexuses of the pyloric region interrupt the function of gastric peristalsis of the fundus and the antrum, causing a disturbance of gastric emptying. Therefore, we believe that the condition should be called achalasia of the pylorus rather than hypertrophic stenosis of the pylorus.

Diseases of the digestive tract due to pathologic changes of the myenteric plexuses can be classified in three different groups: (1) conditions due to agenesis of the myenteric plexuses: congenital megacolon (Dalla Valle, Swenson and associates, and Ehrenpreis), and congenital megaduodenum (Barnett and Wall); (2) conditions due to reversible alterations of the myenteric plexuses (hypertrophic stenosis of the pylorus in the newborn); (3) conditions due to irreversible lesions of the myenteric plexuses (acquired megaesophagus, acquired megacolon, acquired achalasia of the pylorus, and acquired megaduodenum).

Would these three groups of diseases be caused by the same etiologic factor? The difference in the plexus lesions observed do not

favor this theory; it is possible that each condition has a different etiologic agent. With reference to acquired megaesophagus, megacolon, achalasia of the pylorus, and megaduodenum seen in our country, many authors believe that the plexus lesions are caused by Chagas' disease.

SUMMARY

The histopathologic changes of the myenteric plexuses were studied in 5 newborns and in 8 adults with hypertrophic stenosis of the pylorus. In the newborn slight alterations of the neurons were found which were considered reversible. In the adult definite lesions of the ganglion cells were noted which in many cases led to complete destruction of the neurons forming the plexuses and which were replaced by newly formed connective tissue. The muscles of the antrum were always hypertrophic in the newborn, while only sometimes in the adult.

Based on these findings, the pathogenesis of the condition in the adult and the infant was explained on the basis of Hurst's theory of achalasia. Hence, it is better to call the condition achalasia of the pylorus of the newborn and of the adult. The etiology seems to differ in children and adults. In children changes in the nerve cells are reversible, as the literature contains reports of spontaneous cures and cures brought about by medical treatment. The observations of Wollstein and Miller on patients submitted to pyloromyotomy by the technique of Fredet-Ramstedt also favor this reasoning. Lesions in the adult are irreversible. The best treatment in the adult is by the pyloroplasty of Finney.

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DIRECT VISION REPAIR OF TRIATRIAL HEART AND TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

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SINCE HYPOTHERMIA provides an effective and relatively safe method of repairing atrial septal defects under direct vision it is logical that the technique should be applied to more difficult intracardiac defects. In repairing 41 atrial septal defects (exclusive of the so-called atrioventricular canal or incomplete double heart) we have had 5 operative deaths. Among the last 35 operations there have been only 3 deaths. Using hypothermia and direct vision repair, Swan has had similar results (13). He has also described a successful application of the method to correct pulmonary stenosis under direct vision (14). The method has, in addition, found application for repairing other intracardiac defects experimentally. In dogs we have used it successfully to repair ventricular septal defects (5), and aortic pulmonary septal defects (12), and to operate on the aortic[1] or pulmonary valves under direct vision. It has also been a satisfactory experimental method for operating upon the mitral valve under direct vision (11).

At the present time, hypothermia appears to have established a potential value for repairing atrial septal defects, pulmonary stenosis, ventricular septal defects, aortic pulmonary septal defects, aortic stenosis, and possibly mitral insufficiency under direct vision. This report shows how it may also provide an excellent way for repairing 2 rare intracardiac defects.

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[1] Recently we have successfully relieved a case of congenital aortic stenosis in a child under direct vision during hypothermia.

In a relatively short period of time, we have encountered 2 unusual congenital anomalies which produce dissimilar clinical manifestations but which have a somewhat similar embryologic origin. They both represent an abnormal joining of the pulmonary veins and the atria. One of these anomalies was a triatrial heart and the other, total anomalous pulmonary venous drainage with entry of all the pulmonary veins into the right atrium. To our knowledge, successful repair of these anomalies has not been previously reported.

Total anomalous pulmonary venous drainage. In this defect, there is an abnormal drainage of the entire pulmonary venous blood flow into the right side of the heart. Usually all of the veins from both lungs join to form a single large vein which then enters into the right atrium or one of its tributaries. If the anomalous drainage is not directly into the right atrium it is into one of the veins or structures which originate from the primitive cardinal or splanchnic venous systems. Most commonly this is the superior vena cava or a major tributary of the superior vena cava while drainage directly into the right auricle is probably the second or third most common site. In his excellent review, Brody found 23 cases of total anomalous pulmonary venous drainage in which there were no associated cardiac defects of importance other than a patent foramen ovale. Among these 23 cases, the anomalous veins entered the superior vena cava or its tributaries in 8, the coronary sinus in 7, the right atrium in 3, the portal vein in 2, the inferior vena cava in 1, partly into the superior vena cava with the remainder into the right atrium in

TABLE I.—CARDIAC CATHETERIZATION IN CASE 1, TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE

	February 1952		*May 1954*
	Pressure, mm. Hg	*Oxygen content, vols. per cent*	*Oxygen content, vols. per cent*
Pulmonary artery	34/10	13.9	—
Right ventricle	34/2	14.4	—
Right atrium	18/13	14.7	14.4
Left atrium	16/11	15.0	15.1
Pulmonary vein	—	15.8	—
Superior vena cava	—	—	12.5
Inferior vena cava	—	12.1	—
Innominate vein	—	10.0	—
Brachial artery	—		15.3

1, while in 1 fetus the drainage was into the duct of Cuvier.

Total anomalous pulmonary venous drainage carries a poor prognosis. In Brody's review, for example, among 37 cases with total anomalous pulmonary venous drainage of all types, he found only 8 that lived beyond the age of 6 months.

In this condition, there is peripheral desaturation, often severe enough to cause cyanosis, which is due to a mixing of venous and oxygenated blood in the right atrium. The only blood received by the left atrium is that which flows through the patent foramen ovale. Right heart failure, provoked by the excessive volume recirculated, occurs in time and the cyanosis deepens.

When the disease is unassociated with other major anomalies, repair would seem to be feasible. In some types of the disease, such repair would involve transplantation of the common pulmonary vein to the small left atrium with subsequent closure of the atrial septal defect. Such a procedure has been described by Bailey but no actual use of the operation has been reported.

Triatrial heart. In this rare anomaly the left atrium is divided by a septum into two chambers—a posterior-superior chamber into which all of the pulmonary veins enter, and an anterior-inferior chamber which leads into the left ventricle through a normal mitral valve. The auricular appendage forms part of the anterior-inferior chamber. Dependent upon the completeness of the septum, Loeffler has divided the anomaly into three types. In the first type there is no communication between the upper and lower chambers, though there may be an opening from the upper chamber into the right atrium. Death occurs in infancy. One or more small openings occur in the septum in the second type, while the septum forms only a partial division between the chambers in the third type.

The severity of symptoms caused by the malformation depends, in the second and third types, upon the size of the opening in the septum and upon whether or not there is an associated defect of the foramen ovale. In individuals with a large communication there may be no symptoms and the defect may be discovered only as an incidental finding at autopsy. On the other hand, if the opening is small enough to cause a significant obstruction to pulmonary outflow, pulmonary congestion and heart failure will occur, producing a clinical picture similar to that caused by mitral stenosis. This clinical picture was found in the first recorded instance of this defect, described by Church in 1868. When there is a patent foramen ovale associated with the defect the clinical picture becomes more confusing, for then there is a peripheral desaturation.

Several theories have been advanced to explain the embrylogic development of the anomaly but perhaps the most appealing, especially in those cases in which the foramen ovale has closed normally, is that advanced originally by Griffith and later supported by Loeffler and others. They explain the defect as a failure of the embryonic common pulmonary vein to incorporate normally into the posterior part of the left atrium. This third chamber, then, is actually the dilated common pulmonary vein.

TECHNIQUE OF HYPOTHERMIA

The method of body cooling that we employ for intracardiac surgery has been described previously (6, 7) but since some modifications which now are part of the technique were used in these cases, a short description of the method with emphasis on these modifications will be given.

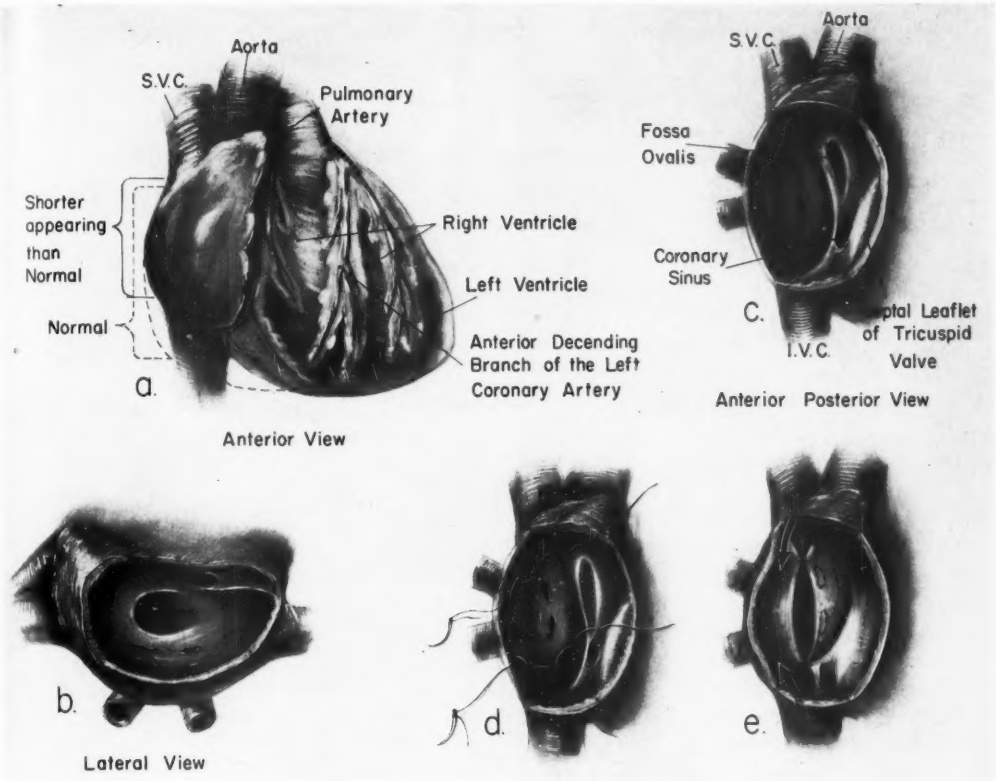


FIG. 1. Total anomalous pulmonary venous drainage with entry of all pulmonary veins into the right atrium (Case 1). These illustrations were drawn from memory. a, General appearance of the heart from the front. The right atrium and right ventricle were enlarged. b, Right atrium opened. The 4 pulmonary veins enter into the posterior part of this chamber. Several small openings in the fossa ovalis represent the only channel by which blood enters the left heart. c, Another view of the opened right atrium. d, A large opening has been made in the atrial septum and the upper and lower repair stitches have been placed. e, The first 2 repair stitches have been tied. The remaining opening between them was closed with a running stitch.

During the entire cooling period, the thoracotomy, and the first part of the rewarming, the patient is attached to an automatic respirator and given a mixture of 5 per cent carbon dioxide in oxygen. During the latter part of rewarming this respiratory mixture is changed to 100 per cent oxygen. A constant rate and depth of respiration is maintained throughout. The respirator consists of an electronic timing circuit which controls inspiratory and expiratory solenoid valves and it employs an open system. With this apparatus the rate and volume of respiration are controlled and the blood hydrogen ion concentration is thereby maintained at a constant level, slightly below normal. Experimentally, this sytem of respiratory control has lowered the incidence of ventricular fibrillation during profound hypothermia (9), and this observation appears to have been born out clinically as well. Among the 13 patients so far subjected to open intracardiac surgery with this respiratory system, there has been only 1 instance of ventricular fibrillation (in a 54 year old man with an atrial septal defect,

TABLE II.—CARDIAC CATHETERIZATION IN CASE 2, TRIATRIAL HEART

	Pressure mm. Hg	*Oxygen content, vols. per cent*
Pulmonary artery	36/15 (Mean 22.5)	15.6
Right ventricle	35/2.5	14.8
Right atrium	2.5	15.0
Superior vena cava	—	13.1
Femoral artery	—	19.8

pulmonary hypertension, and coronary sclerosis). Previously, this complication occurred in about 30 per cent of our patients (7).

Enough anesthesia is given to prevent shivering, muscular tremor, or any respiratory effort during cooling. Thiopental plus a curare drug have been used and heavier doses are given than were used early in our experience with hypothermia. The patient with the triatrial heart, for example, had 30 milligrams of thiopental per kilogram of body weight while the boy with the total anomalous pulmonary venous drainage had 54 milligrams per kilogram.

When the body temperature has fallen to 30 degrees C., after 1¼ to 3¼ hours of surface cooling with refrigerating blankets, the cooling is stopped and the thoracotomy commenced. The body temperature drifts down reaching a low point of 26 to 28 degrees C. during the operation.

For rewarming, the patient is immersed in a bath of hot water at 45 degrees C. after the chest has been closed. When the temperature reaches 35 degrees C., after ⅓ to 1½ hours in the bath, he is taken out.

CASE REPORTS

Total Anomalous Pulmonary Venous Drainage

CASE 1. This patient was a 5 year old boy in whom a murmur had been detected at the age of 6 months. At the age of 18 months a cardiac catheterization was done which did not lead to a complete diagnosis; it did, however, demonstrate an atrial septal defect and both a left to right and a right to left shunt. The cardiac catheterization was repeated in May 1954. Again, the atrial septal defect was located by passing a catheter into the left atrium, and this plus the relatively desaturated blood in the left atrium and a higher oxygen saturation of the peripheral arteries than was found in the right atrium suggested the possibility of anomalous pulmonary venous drainage (Table I). After reviewing all the data a diagnosis of total anomalous pulmonary venous drainage with all the pulmonary veins entering the right atrium was made by the pediatric cardiologists.

The child was mildly cyanotic and his strength had decreased during the year prior to his operation. His heart was large and the edge of his liver was 10 centimeters below the costal margin.

On June 7, 1955 he was anesthetized and cooled in preparation for a thoracotomy. When the rectal temperature had fallen to 29 degrees C. the cooling was stopped and the chest was opened but the body temperature continued to fall reaching a low point of 25 degrees C.

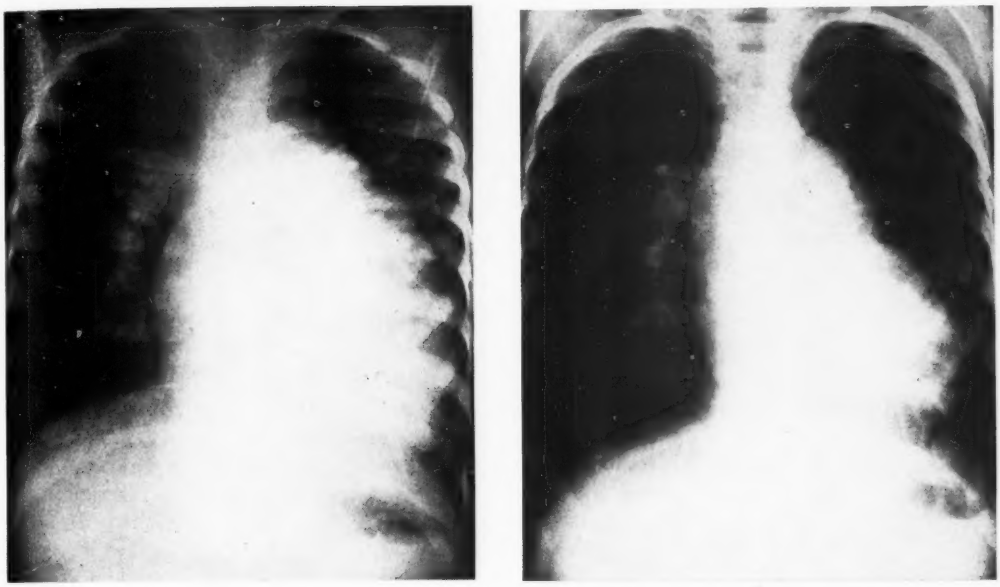
After the heart had been explored by inserting one finger into the right and one finger into the left atrium simultaneously, the circulation was occluded and the right atrium was opened widely to expose the anomaly which is illustrated in Figure 1. As the first step in repair the small atrial septal defect was enlarged and after this the right atrium was reconstructed so that the pulmonary veins were directed through the atrial septal defect into the left atrium while the superior and inferior venae cavae retained their openings into the right atrium (Fig. 1d and 1e). The atrium was closed and circulation was resumed after a total occlusion period of 6 minutes.

Immediate convalescence was satisfactory except for a brachycardia (pulse rate of 60 to 70) which appeared to be due to digitalis overdosage. The brachycardia did not disappear on discontinuing digitalis, however, and so with the signs of beginning heart failure, digitalis was restarted. The slow heart rate persisted with a nodal rhythm or a wandering atrial pacemaker indicated on the electrocardiogram. Finally, 2 months postoperatively the digitalis was stopped again following which his heart rate returned to normal with a sinus rhythm.

The clinical improvement since surgery has paralleled the improved x-ray appearance shown in Figure 2.

Triatrial Heart

CASE 2. This 23 year old man complained of some loss of physical stamina but no serious disability when he was admitted for cardiac catheterization in August 1954. On examination a soft systolic murmur along the left sternal border was heard by some, but not all, examiners. On x-ray examination, the heart was not generally enlarged though there was some prominence of the left atrium and the main pulmonary trunks. There were small discrete stippled densities in both lung fields suggestive of hemosiderosis. The cardiac catheterization findings are shown in Table II. There was an increase in oxygen saturation of almost 2 volumes per cent between the vena cava and the right atrium. This observation was not completely satisfactory evidence, but nonetheless, a tentative diagnosis of atrial septal defect was made.



a b

FIG. 2. Case 1, the 5 year old boy with total anomalous pulmonary venous drainage. Chest roentgenograms taken: a, before, and b, 4 months after surgery.

No special treatment was advocated at that time and the patient got along well until March of 1955 when cardiac decompensation, manifested chiefly by pulmonary congestion, occurred. When he recovered from this, surgery was recommended.

The operation was done on May 24, 1955. After 1 hour and 15 minutes of cooling, when the patient's temperature had fallen to 30 degrees C., the sternum was divided transversely and both pleural cavities opened widely through the fourth interspaces.

In contrast to the first case, an accurate anatomic diagnosis at the operating table proved to be difficult, but it was finally made before doing the open cardiotomy. The right heart and pulmonary artery were abnormally large but no thrills could be palpated. Following an external examination, the interior of the right heart was explored by inserting a finger into the right atrium through the atrial appendage. We were perplexed to find no atrial septal defect, but a tense chamber could be palpated posterior to and slightly higher than the right atrium. Assuming that this was the left atrium, we concluded that the patient had mitral stenosis so a finger was inserted into the left atrium but the mitral valve was normal.

Further exploration followed and finally led to the diagnosis. One bare index finger was inserted in the left atrium and another simultaneously probed in the right. The presence of an intact atrial septum was adequately confirmed with this examination, but more important, we found during this examination that there were no pulmonary veins entering the left atrium though there appeared to be a single narrow opening entering that atrium high and to the right. With the bidigital examination neither finger entered the tense posterior chamber, which had a pressure on needle exploration of 35 centimeters of water.

After all this exploration a diagnosis of triatrial heart was tentatively made and further confirmed by noting that the finger in the left atrium could push one wall of the left atrium (actually the septum between the two chambers of the left atrium) back into the tense posterior chamber (Fig. 3).

We decided to make an opening in this septum under direct vision and began by elevating and separating the right atrium from the third chamber to expose it (Fig. 3d). With one finger still in the left atrium the cardiac inflow and outflow were occluded and an opening was made into the third chamber from the right. By pushing the finger in the left atrium back and to the right the abnormal septum was demonstrated clearly (Fig. 3e) and an opening 2.5 centimeters in diameter was cut in it. The wound in the third chamber was then closed and circulation was resumed after an occlusion period of 3½ minutes.

The patient was rewarmed and his subsequent convalescence was uneventful. Seven months following surgery his general health was excellent though he had suffered 3 short bouts of what was apparently paroxysmal ventricular tachycardia, the last 3½ months after his operation. On examination no abnormalities

could be found and the pulmonary vascular marking and heart shadow were smaller than they had been preoperatively.

DISCUSSION

Both of the defects described are rare but with an increasing general interest in the surgical treatment of congenital cardiac anomalies they are certain to be detected more frequently than they have been in the past. Once they are recognized many of them can be repaired.

It is quite likely that all cases of triatrial heart could be repaired by the technique we described but at least one modification of this operation should be worth while. The incision made in the abnormal septum dividing the two chambers of the left atrium could doubtless have been safely extended up to the small opening that already existed between these chambers, thus making a larger opening than the one we created. We reached this conclusion after reviewing published reports on the anatomy of the defect. Without this knowledge of the detailed pathologic anatomy at the time of the operation we feared that an incision larger than the one we made might have carried us outside of the heart.

Another addition to the technique might have helped us to learn more about the precise configuration of the septum, prior to the open cardiotomy. The abnormal septum could have been examined with one finger in the third chamber while a finger of the other hand was still in the left atrium. Because the third chamber had a high pressure and little available surface for entry we did not try this. Had we made this exploration, however, another possibility might have arisen—that of cutting the septum blindly with a knife on the end of one finger, rather than the method described of dividing it under direct view through an open cardiotomy. Putting aside these retrospective considerations, at the operating table the open method appeared to be a logical one; it was simple and direct, and we shall use it again when the opportunity arises.

The need for an open operation is even more convincing in the patient with total anomalous pulmonary venous drainage. Here it was necessary not only to divide a septum, but, in addition, we had to reconstruct the right atrium accurately.

This particular type of anomalous pulmonary venous drainage, in which all the pulmonary veins enter the right atrium, proved in agreement with our preoperative concept to be suitable for an open repair. It is quite likely that cases in which all the pulmonary veins drain into the coronary sinus could be similarily repaired. The venous blood from the coronary system would then drain into the left atrium, but this defect is doubtless a minor one. The technique described offers nothing for the cases in which all the pulmonary veins enter the superior vena cava or other systemic veins. Superficially, these cases would seem to be easier to correct than the defect described in this article, but because of the difficulties of achieving a satisfactory venous anastomosis they may, in fact, be more difficult.

Since both of these unusual and complex repairs were done with the aid of hypothermia we would like, once more, to recommend hypothermia for open intracardiac surgery. Mechanically, hypothermia provides what is clearly the least encumbered method of operating within the heart. The hazards of pumping blood outside of the body are avoided. The operating field is truly bloodless during the repair and the heart action is slow. The instrumental requirements are relatively simple and, therefore, a mechanical breakdown is not apt to cause a disaster. Finally, only a small operating team is required, and thus, only a few individuals face the responsibility of being able to cause a tragic human error.

One weakness of the technique has been the limited time permissible for the open cardiotomy. It may be possible to use deeper levels of hypothermia or supplementary perfusion techniques (9, 10) which will permit more time within the heart, but even

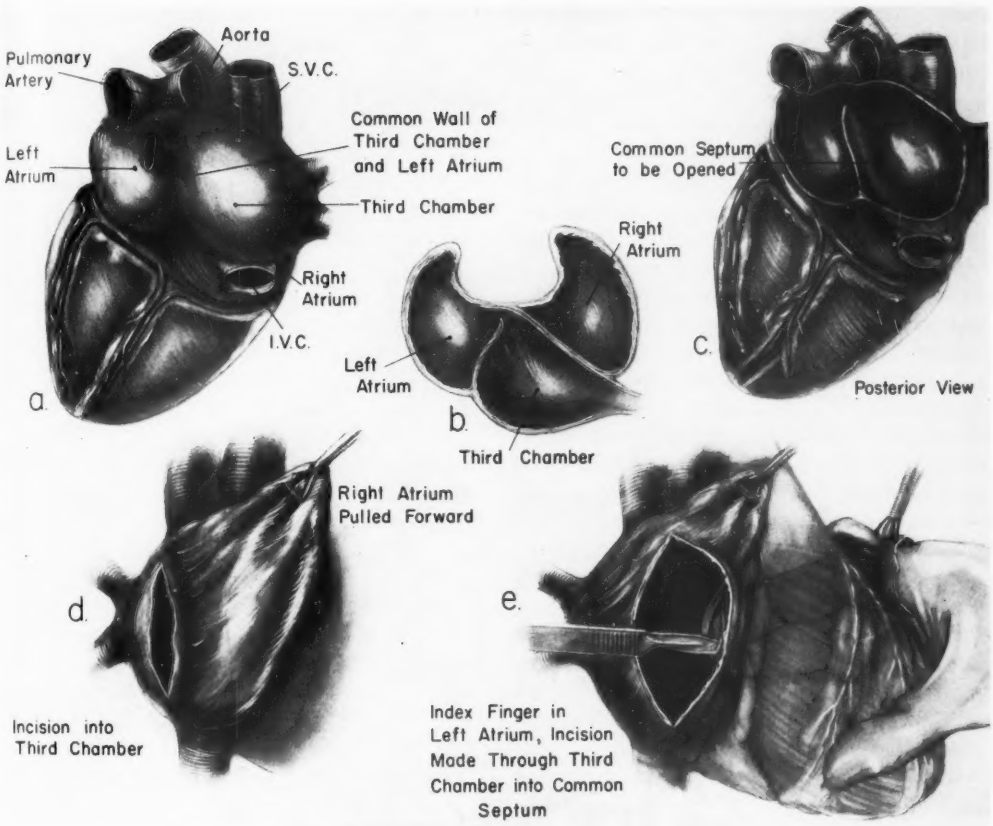


FIG. 3. Triatrial heart in a 23 year old man (Case 2). As in Figure 1, these illustrations are essentially diagrammatic for no sketches or photographs were made at the operating table. a, View of the heart from behind showing the position of the third chamber and its relationship to the small left atrium, or anterior chamber. All pulmonary veins enter the third chamber. b, Coronal section illustrating the posterior position of the third chamber. c, Another posterior view illustrating the approximate position of the abnormal septum. d, In order to open the third chamber anteriorly the right atrium was elevated and reflected to the left. e, A finger is in the left atrium and the third chamber has been opened widely under inflow occlusion. With this exposure a large opening was made in the abnormal septum.

without these refinements the handicap of time limitation can be largely overcome. The operation carried out on the patient with anomalous pulmonary veins demonstrated that it is quite possible to finish complex repairs well within a safe occlusion period. However, detailed plans for the repair must be made before the circulation is occluded and these plans cannot be made unless the pathologic condition is examined first with an exploring finger, or in special cases like the 2 described in this paper, with two fingers, one in either side of the heart. If instruments and sutures are inspected and each person at the operating table understands his duties, confusion, haste, and useless motion can be reduced and time saved. With the advantage of a completely dry field that total circulatory occlusion provides, and with the studied employment of reasonable time-saving techniques, it may be that all or nearly all repairable intra-

cardiac defects can be repaired within 8 or 10 minutes. When it becomes possible to transplant cardiac homografts successfully, of course, more time will be needed.

A more serious weakness than the time limitation has been the tendency to ventricular fibrillation associated with hypothermia. It may be impossible to eliminate this hazard especially in patients with enormous hearts and arrhythmias, but there has been some improvement. Both in animals (9) and man this complication has apparently been less frequent since an automatic respirator employing 5 per cent carbon dioxide in oxygen with an open system has been employed. A gentle operating technique also protects the cold heart against fibrillation.

SUMMARY

1. A case of total anomalous pulmonary venous drainage in a 5 year old boy was repaired in one stage through an open cardiotomy. With the right atrium open, the atrial septal defect was enlarged and then the right atrium was reconstructed. Prior to the reconstruction all four pulmonary veins entered the posterior part of the right atrium but afterward they were directed through the atrial septal defect into the left atrium.

2. A triatrial heart in a 29 year old man was also corrected by means of hypothermia, inflow occlusion, and an open cardiotomy. The third atrial chamber was opened while a finger in the left atrium invaginated the abnormal septum into the third chamber. This septum was then divided under direct vision.

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SURGICAL MANAGEMENT OF DIVERTICULITIS

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FOR MANY YEARS, surgical intervention in the treatment of diverticulitis of the colon has been limited to the treatment of its complications—obstruction, perforation, and fistula formation. Many surgeons still believe that these complications represent the only indication for operation in the treatment of this condition. Most of our textbooks of surgery advise surgery only for the complications of diverticulitis. A recently published work on the surgery of the alimentary tract contains an excellent summary of current surgical opinion on the treatment of diverticulitis, but Shackelford introduces the subject with the words ". . . surgery being reserved for those subjects who have complications."

The surgical management of these complications of diverticulitis is associated with a high morbidity rate, a significant mortality rate, and a long period of disability for the patient. It requires prolonged and expert surgical care to bring an elderly, obese patient through an acute abdominal emergency caused by perforation or complete obstruction of the large intestine. If he survives this illness he still faces a period of months with a colostomy, a major operative procedure for resection of the diseased bowel, and a third operative procedure for closure of the colostomy. The same is true for the patient who walks into his physician's office with the complaint that he has been passing gas through his urethra. Although he may not be acutely ill, his colovesical fistula is associated with an extensive inflammatory reaction involving his bladder and colon; it will probably require the same multiple operative procedures, repeated hospitalization, and long period of disability before it is corrected.

One of the achievements of modern surgery has been the virtual elimination of staged operations for the resection of carcinoma of the colon. Surgeons have begun to question the need for staged operative procedures in the treatment of any surgical lesion involving the large bowel. Have modern surgical techniques, multiple blood transfusions, and particularly the availability of many different types of antibiotics changed the picture so far as these complications of diverticulitis are concerned?

Much credit has been given to the antibiotics for the low morbidity and low mortality rate in resection of the colon for carcinoma. Yet McKittrick and others have shown that resection of the colon can be carried out with comparable mortality and morbidity rates, without using antibiotics at all. Moreover, anyone dealing with surgical infections in recent years must have been impressed with the increasing prevalence of bacteria which are partially or completely resistant to antibiotic therapy. Surgeons have realized that only by adherence to fundamental surgical principles can we maintain the present low morbidity and mortality rates associated with modern surgical practice. This fact is especially true for an inflammatory lesion of the colon associated with perforation or obstruction.

Two important surgical principles are involved in the surgical treatment of these patients: (1) the acute inflammatory reaction surrounding a perforation of the colon will tend to subside if that segment of the bowel is defunctionalized by a proximal colostomy, and (2) resection and primary anastomosis of a distended, obstructed colon is dangerous. Boyden has urged the more frequent use of a one stage operative procedure for diverticulitis but would limit it to those cases in which the inflammation has subsided or is limited to the bowel, not associated with abscess or obstruction. Welch, Allen, and Don-

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TABLE I.—PATIENTS OPERATED UPON FOR DIVERTICULITIS

	1948–1953	*1953–1956*
Number	50	40
Sex—males, per cent	62	60
Average age, yrs.	53.5	58.8
Pain, per cent	74	100
Change of bowel habit, per cent	35	35
Constipation, per cent	72	90
Gross bleeding, per cent	22	5
Average duration, yrs.	3⅛	1–12 in 72.5 per cent

aldson have advised a one stage procedure for diverticulitis, but only if the patient is in good condition, has normal chemical findings, and does not have obstruction, perforation, or a fistula.

An acute inflammatory lesion of the colon, associated with complete obstruction, perforation, or a fistula is a serious surgical problem. Resection of the colon under these conditions is a hazardous procedure. There is little doubt that a proximal colostomy, followed by resection of the diseased bowel after sufficient time has elapsed to allow the acute inflammatory process to subside, will give these patients a better chance to survive.

Patients with diverticulitis of the sigmoid can be operated upon safely, if the operation is performed before complications develop. Many surgeons have demonstrated that segments of the colon, with chronic, subacute, or even acute diverticulitis, can be resected safely in a one stage operative procedure. Some of these patients will have small abscesses within or adjacent to the bowel or its mesentery. The success of this procedure necessarily involves good judgment in the selection of cases, careful but adequate dissection at the time of operation, and close observation during the postoperative period.

Is it possible to select those patients with diverticulitis who are most likely to develop obstruction or perforation? Many serious abdominal emergencies could be prevented if resection was advised in such cases. The diseased bowel could be removed in one operation with a hospitalization period of less than 2 weeks. The patient would also be permanently relieved of his recurrent abdominal symptoms. It is possible—to a limited extent.

Age may prove to be a significant factor. Welch, Allen, and Donaldson believe that uncomplicated diverticulitis should be considered an important indication for operation in patients under 50 years of age. They pointed out that 18 per cent of all their patients who were operated on for diverticulitis were under 50 years of age, while only 6 per cent of all patients with diverticulitis were in this age group. Our own experience is similar. The average age of a group of 50 patients operated upon who were previously reported from this clinic was 53.5 years. Of the present group, 10, or 25 per cent, were under 50 years of age.

Resection should also be seriously considered in any patient whose attacks of diverticulitis are increasing in frequency or severity. Resection should be advised for any patient in whom barium enema examination reveals an increasing degree of obstruction. The onset of suprapubic pain and dysuria in a patient with diverticulitis usually indicates bladder involvement, and operative intervention at this time may prevent a colovesical fistula.

In many instances, however, it is not possible to recognize those cases in which complications of diverticulitis will develop. These complications may occur before the diagnosis has been made. Perforation may be preceded by acute abdominal symptoms of only a few days' duration. Complete obstruction of the large intestine due to diverticulitis may occur following 2 to 3 weeks of vague abdominal pain and increasing constipation. Only careful questioning may disclose the repeated bouts of mild indigestion which preceded the onset of dysuria and pyuria due to a colovesical fistula.

Adequate examination, including a barium enema study, will reveal the diagnosis in many patients with mild digestive complaints. Having made the diagnosis, we must appreciate the fact that diverticulitis is a potentially lethal disease. It may develop insidiously and it may progress rapidly. If we are going to reduce the mortality and the morbidity associated with treatment of

diverticulitis, surgeons and gastroenterologists must consider surgical intervention in any patient with persistent or recurrent symptoms.

The treatment of diverticulitis is also complicated by the necessity of excluding malignant disease. Carcinoma of the sigmoid may be present along with diverticulitis, or it may present the clinical picture of diverticulitis. Carcinoma involves the sigmoid colon more frequently than any other part of the intestinal tract except the rectum. Practically all diverticulitis occurs in the sigmoid colon. Both diseases tend to occur in patients over 50 years of age and both may be associated with left lower quadrant pain, rectal bleeding, and a change in bowel habit. Both lesions frequently produce obstruction of the colon, and both may lead to a colovesical fistula. At operation, carcinoma, like diverticulitis, may appear as an adherent fixed mass involving the sigmoid colon.

We tend to rely upon the barium enema examination to distinguish one lesion from the other; yet the barium enema film is often equivocal and may actually be misleading. In deciding whether the condition is likely to be malignant or inflammatory in nature (3), a careful review of the history may be helpful. A presumptive diagnosis of either carcinoma or diverticulitis is important. It will have considerable influence upon the operative procedure if a primary resection is to be employed; it is of vital importance if a multiple stage procedure is decided upon.

The clinical records of 40 patients with diverticulitis who came to surgery during the last 3 years have been reviewed. Data which have a bearing on the surgical treatment of these patients will be presented.

CLINICAL DATA

The clinical picture (Table I) in this group of patients is very similar to that presented by a group of 50 patients with diverticulitis who were operated upon during the previous 5 year period and reported by Colcock and Sass. Sixty per cent of this present group and 62 per cent of the previous group were males. The ages of the present group ranged from 30 to 77 years, with an average age of 58.8 years; the average age in the previous group was 53.5 years. Thirteen, or 32.5 per cent, of the present group were markedly overweight, and 4, or 10 per cent, were physicians.

TABLE II.—BARIUM ENEMA EXAMINATION

	1948–1953 *Per cent*	*1953–1956** *Per cent*
Definitely or "probably" diverticulitis	72.0	67.7 (1 carcinoma)
? Diverticulitis ? Carcinoma	16.0	22.5
Complete obstruction	10.0	9.8

*Examination was carried out in 31 of 40 patients.

Pain is a common symptom in diverticulitis. It was present in 74 per cent of the group previously reported and in all of the present group of patients. Pain was usually most marked in the left lower abdominal quadrant; occasionally it was present in both lower quadrants or in the suprapubic region. Recurrent attacks of pain, usually increasing in frequency and severity, are characteristic. A change in bowel habit was a common symptom but less frequent than pain; it was present in approximately 35 per cent of both groups. Diarrhea was present in 10 per cent of this group and in 28 per cent of the previous group.

Hoar and Bernhard have emphasized the frequency of bleeding in patients with diverticulitis. They found it to be present in 42 of 111 cases. It should be noted, however, that the bleeding was occult in 31 of these patients. In our experience, gross bleeding sufficient to come to the attention of the patient is not common in diverticulitis. In the previous study of 50 patients with diverticulitis coming to surgery, gross bleeding was present in 22 per cent. Many of these patients had other possible causes for their bleeding, such as hemorrhoids or polyps. In contrast, 64 per cent of the 50 patients with carcinoma of the sigmoid gave a history of rectal bleeding. Only 2 patients in this present group had noticed rectal bleeding. One of these patients had large hemorrhoids which were obviously causing

FIG. 1. Preservation of mucosal outline along with history of operative findings led to diagnosis of diverticulitis. Adequate follow-up study was not obtained and carcinoma was found at operation a year and a half later.

part if not all of his bleeding; the other patient had a benign mucosal polyp associated with his diverticulitis. As Patterson, Ransom, and others have pointed out, the presence of rectal bleeding in a patient with diverticulitis is an indication to look for some other associated lesion.

One of the most significant differences between the clinical picture of diverticulitis and that of carcinoma of the sigmoid is the duration of symptoms. While patients with diverticulitis may have an acute onset of severe symptoms leading to perforation or complete obstruction within a few days, the average duration of symptoms is appreciably longer than it is in patients with carcinoma of the colon. In the previous study, the average length of time that symptoms were present was 40.2 months for patients with diverticulitis and 8.5 months for those with carcinoma. In the present group of 40 patients, 29, or 72.5 per cent, had had symptoms referable to their diverticulitis from 1 to 12 years. Symptoms had been present for less than a month in 4 patients and from 1 to 10 months in 7 patients. Patients with colovesical fistula usually have bouts of chills, fever, dysuria, and pyuria. Occasionally dysuria will develop when the inflammatory mass is adherent to the bladder, although an actual fistula is not present. Nausea and vomiting, with periumbilical cramplike pain, may be present if the inflammatory mass becomes adherent to the small bowel. Obstruction of the small intestine was present in 3 patients in this group. On physical examination most of these patients had tenderness in the left lower abdominal quadrant. This tenderness was less marked, of course, in those patients who had previously had a colostomy. Distention was present in patients with acute obstruction and a mass was palpable in the left lower quadrant in 4 patients.

TABLE III.—OPERATIVE FINDINGS IN 40 PATIENTS

		No. of cases
Polyps (1 malignant)		4
Perforation—38 operations		
Fistulas (7), peritonitis, or abscess		16
Obstruction		6
Small bowel	3	
Sigmoid	3	
Miscellaneous		4
Foreign body	1	
Scrotal abscess	1	
Carcinoma	1	
Ulcerative rectal lesion	1	

ROENTGEN EXAMINATION

A barium enema examination was carried out in 31 of these 40 patients (Table II). It was omitted in a few patients who had an acute onset of their illness and in some of the patients who already had a colostomy. In 21 of the 31 patients who had barium enema examination, a definite diagnosis of diverticulitis was made. It is significant, however, that 1 of these 21 patients proved subsequently to have carcinoma, and the erroneous interpretation of the barium enema film was responsible for a long delay in the recognition and treatment of the cancer (Fig. 1). This patient was finally operated upon because of an increasing degree of obstruction, and even at operation the mass in the sigmoid was thought to be diverticulitis. In 7 of the 21 patients, perforation of the bowel was noted on the x-ray film (Fig. 2). Although perforation may occur as a result of carcinoma of the sigmoid, perforation and fistula formation

are much less common than in patients with diverticulitis. In the previous study, 6 per cent of the patients with carcinoma had a perforation and 1 patient had a fistula into the bladder. Of the 50 patients with diverticulitis in that report, 40 per cent had had a perforation and 34 per cent had formed an internal or external fistula. In 7 patients, or 17.5 per cent, of the present group, the roentgenologist was unable to exclude carcinoma on the barium enema examination, and in 2 patients a diagnosis of "probably carcinoma" was made. In 3 additional patients, the sigmoid colon was found to be completely obstructed, but the cause of the obstruction could not be outlined by the barium enema.

FIG. 2. The numerous diverticula, the length of the defect, and the extravasation of barium indicating perforation all suggested diverticulitis. The sharp demarcation plus some suggestion of "lipping" makes it impossible to exclude carcinoma definitely. At operation the patient had diverticulitis which had perforated, forming an abscess between the bowel and the bladder.

OPERATIVE FINDINGS (TABLE III)

Four patients had polyps associated with diverticulitis. In 1 case the polyp was already malignant. There was no invasion of the base of the polyp, and examination of the resected specimen showed no metastasis in the mesenteric lymph nodes (Fig. 3).

There were 16 patients with perforation. One patient with a 3 day history of severe abdominal pain associated with marked abdominal distention was found to have a spreading peritonitis at the time a colostomy was established. Fifteen patients had an abscess or a fistula secondary to a perforation of their diverticulitis. One of these 15 patients had a history of abdominal symptoms for 2 weeks; the other 14 had had attacks of left lower quadrant pain for at least 1 year. Before they were discharged from the hospital for the last time the 16 patients with perforation had had a total of 38 separate operative procedures for the relief of their diverticulitis. (Ten patients had had 1 or more operative procedures for their diverticulitis before coming to the clinic.)

There were 3 instances of a colovesical fistula. One patient gave a history of 6 months' duration; the other 2 had had symptoms of diverticulitis and cystitis for many years. One of these 2 patients had continued to have attacks of dysuria and pyuria even though a proximal colostomy had been present for 4 years. There were 2 instances of a colovaginal fistula. One had followed the local excision of a diverticulum of the sigmoid at the time of hysterectomy; the other had occurred spontaneously after several months of conservative treatment of her diverticulitis (Fig. 4). There were 2 instances of fistula between the colon and the ileum. One patient had an acute onset of symptoms; the other patient had had attacks of cramplike pain for 4 years. An ileocolocutaneous fistula followed the release of adhesions between the ileum and colon 3 months before admission to the clinic.

There were 3 patients with small intestinal obstruction. One had been ill for 8 days

FIG. 3. Barium enema film showing evidence of partial obstruction in addition to a well outlined polyp in the same area. At operation the sigmoid was found to be thickened and contracted because of diverticulitis. It also contained a malignant polyp.

and the other 2 had had symptoms for years. Three patients had had complete obstruction of the sigmoid colon. Two gave a short history of 1 month. The third patient had had 3 operative procedures for relief of his diverticulitis. Because of extensive scarring in his pelvis, the diseased bowel could not be resected and he was left with a permanent colostomy.

Other complications included the following:

1. One patient who had had attacks of indigestion for many years had swallowed a dental bridge which remained lodged in the diverticulum until it was removed 5 weeks later.

2. One patient developed what was thought to be a strangulated left scrotal hernia. The hernia which had been present for many years had been irreducible for 5 days, and his scrotum had become distended and painful. At operation, a scrotal abscess was found secondary to diverticulitis of the sigmoid in a sliding hernia (2).

3. Carcinoma and diverticulitis were found in 1 patient who gave a history of having had pain in the left lower abdominal quadrant for 2½ years. He had been hospitalized twice. On the second hospitalization a laparotomy was performed, at which time a diagnosis of acute diverticulitis was made. A barium enema examination was interpreted as showing diverticulitis (Fig. 1). He had no rectal bleeding at any time but continued to have recurrent pain in the left lower quadrant and constipation. Eighteen months later at operation an adherent inflammatory mass was found in the sigmoid colon and was resected. It proved to be a large adenocarcinoma with metastases to the regional lymph nodes.

4. Another patient had an ulcerating lesion of his rectum. The lesion measured 3 to 4 centimeters in diameter and was fixed and hard. The surrounding tissues were indurated and the ulcer had a raised, firm, irregular border. A diagnosis of carcinoma of the rectum was made, but a biopsy was negative for malignancy. At operation the ulcer was found to be secondary to an inflammatory mass in the sigmoid which had prolapsed into the pelvis and had become adherent to the ampulla of the rectum. The sigmoid mass was resected and proved to be diverticulitis. The inflammatory process in the rectal wall subsided and the ulcerated area healed.

TABLE IV.—OPERATIVE PROCEDURE IN 40 PATIENTS

	No. of patients	*No. of complications*	*Mortality*
One stage resection	23	5	0
Colostomy (? incision and drainage), resection	13	0	0
Colostomy	2	0	0
Laparotomy	1	0	0
Colotomy	1	0	0

OPERATIVE PROCEDURE (TABLE IV)

Twenty-three patients had an acutely inflamed sigmoid colon not associated with complete obstruction, a fistula, or a large

abscess due to perforation. All were operated upon by a one stage resection, with primary anastomosis. Thirteen patients had another operative procedure in addition to resection, usually incision and drainage of an abscess, or a colostomy, or both. One patient had a colotomy for a foreign body; another had a laparotomy with the release of small bowel adhesions. An elderly patient who had had a colostomy because of an acute perforation of a diverticulum had a simple closure of the colostomy without resection. She has remained well 1 year after operation. One patient was left with a permanent colostomy.

MORBIDITY AND MORTALITY

One patient had a cerebrovascular accident during the postoperative period but survived; in another a postoperative cutaneous fistula developed which closed spontaneously. One patient required incision and drainage of a pelvic abscess; 2 patients had wound separation. It should be noted that all 5 patients with complications had had a primary one stage resection of their diseased colon; all had had symptoms of diverticulitis for years. There were no hospital deaths, although the patient with the permanent colostomy died of a cerebrovascular accident 1 month after discharge.

OPERATIVE TECHNIQUE

A proximal colostomy is established in all patients with complete obstruction, perforation, or a fistula. This colostomy is placed in the proximal portion of the transverse colon so as not to interfere with mobilization of the splenic flexure at the time of resection. The bowel is completely divided whether it is exteriorized simply as a loop colostomy or as a double barrel Mikulicz spur. If an abscess is present in the left lower quadrant, it is incised and drained at the same time. Unless the patient is a poor operative risk, the colostomy is always followed by resection of the sigmoid colon. Recurrence of symptoms is likely to follow closure of the colostomy without resection.

FIG. 4. Barium enema film showing a long narrowed area in the sigmoid with extravasation of barium into the fistulous tract leading to the vagina. She had been treated for diverticulitis for several months before the fistula developed.

If carcinoma can be excluded, resection of the involved sigmoid is carried out 3 to 6 months after the colostomy. At this time all of the acute inflammatory reaction will have subsided and the resection can be carried out with minimal morbidity and mortality. If malignancy cannot be excluded, the involved colon must be resected within 2 to 3 weeks. At this time, most of the inflammatory reaction will still be present and the left ureter and bladder may be firmly adherent to the inflammatory mass.

Patients who have not yet developed complete obstruction, perforation, or a fistula are operated upon by a one stage resection with primary anastomosis. The type of resection depends upon whether the surgeon believes the lesion to be benign or malignant. If the diagnosis is diverticulitis, the bowel and its mesentery are resected so as to preserve the superior hemorrhoidal

artery. If, on the other hand, it is thought that the lesion is malignant, resection of the mesentery should include the inferior mesenteric and superior hemorrhoidal arteries in spite of the associated inflammatory reaction. Malignancy should be excluded before the mesentery of the bowel is divided.

When the diagnosis of diverticulitis is still not certain, it may be possible to exclude carcinoma by a simple technical maneuver. With the mobilized colon depressed into the pelvis, one can often reach the involved segment with the index finger of the left hand inserted into the rectum. Careful palpation of the mucosal surface will usually determine the presence or absence of carcinoma. If no ulceration is felt, the adjacent mesentery can be clamped and divided, with reasonable assurance that malignant cells will not be spread through the operative field.

In diverticulitis it is safe to be conservative as far as the resection of the mesentery is concerned but not with respect to the diseased bowel. Resection through a segment of colon containing diverticula not only invites recurrence of the diverticulitis but sutures placed through diverticula are likely to result in postoperative leakage at the line of anastomosis. The resection should include most, if not all, of the colon containing diverticula. In most patients this will mean mobilization of the splenic flexure and anastomosis of the descending colon to the rectosigmoid. In patients with a colovesical fistula, placing the omentum between the anastomosis and the bladder may help to prevent recurrence of the fistula, should further diverticulitis develop.

A complementary cecostomy or colostomy is carried out only when there is a question regarding the integrity of the anastomosis. A drain is inserted into the operative field in most patients. If a colostomy is established or is already established, it is closed in 1 to 2 weeks.

SUMMARY AND CONCLUSIONS

The cases of 40 patients operated on for diverticulitis during the last 3 years have been reviewed.

Perforation, fistula formation, and obstruction make diverticulitis a serious and possibly a fatal disease. The treatment of these complications involves repeated hospitalization, multiple operative procedures, and prolonged medical and nursing care. This morbidity and mortality can be reduced if these patients are operated upon before these complications develop. Surgical intervention should be considered in any patient with diverticulitis who has recurrent or persistent symptoms.

The presence of carcinoma of the sigmoid must be eliminated in every patient with diverticulitis. Carcinoma is ruled out by the type and duration of symptoms, the barium enema examination, and the findings at laparotomy. The need for excluding carcinoma has a direct bearing on the surgical management of these patients. Diverticulitis of the sigmoid colon may also closely simulate carcinoma of the rectum.

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RECURRENT VARICOSE VEINS

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THE OBJECT OF THIS ARTICLE is to present our observations on the important factors involved in the recurrence or persistence of varicosities in the lower extremity following ligation (usually including resection) and injection treatment for varicose veins.

MATERIAL

Our observations are based on a study of 341 patients who underwent 510 surgical procedures (510 lower extremities) for so-called recurrent varicosity. All patients were reoperated on at the Mayo Clinic in the period from January 1, 1950, through December 31, 1954, by two of us (Lofgren and Myers). All previous operations had consisted of ligation followed by sclerosing therapy except that 2 patients had undergone incomplete stripping procedures. One hundred and twenty-nine of the extremities had been treated at this clinic before we began stripping procedures in 1947, and 2 had undergone incomplete stripping procedures here shortly after 1947. The remaining 379 extremities (74 per cent) were operated on elsewhere. In the last-mentioned group, an operation had been performed only in the region of the groin or behind the knee; this had been followed by sclerosing therapy, but we were unable to determine exactly how extensively such therapy had been used. In the patients treated at this clinic, 3 cubic centimeters of sclerosing solution had been injected retrogradely at the time of operation. This had been followed by multiple injections until the varicosities throughout the extremity were closed.

The 510 extremities included in the study were among a total of 3,319 extremities subjected to stripping of the veins by two of us (Lofgren and Myers) during the 5 years represented by the study; hence the extremities on which our observations are based constitute 15.3 per cent of those treated during the indicated period. The greater saphenous system was affected in 96 per cent of the 510 extremities and the lesser saphenous system in 4 per cent (Table I).

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SURGICAL FINDINGS

Of the 341 patients who underwent a further operation on the veins at this clinic, approximately four-fifths did so within 10 years after the original ligation. The detailed distribution of the patients according to intervals elapsing between the original operation and the stripping procedure was as follows: 0 to 5 years, 36 per cent; 6 to 10 years, 47 per cent; 11 to 15 years, 13 per cent; and 16 years or more, 4 per cent.

Three outstanding characteristics of the so-called recurrent varicose veins were: (1) incompetency of superficial veins below in the thigh, leg, and foot, found in all the extremities, (2) incompetency of perforators, found in a smaller but yet very important number of extremities, and (3) inadequacy of ligation above at the saphenofemoral or saphenopopliteal juncture, found in 61 per cent of all extremities.

Incompetence of superficial veins below. Incompetent superficial veins were present in all extremities operated on, regardless of whether the ligation above had been adequate or not (Table II). Thirty-two patients had undergone 2 previous ligations and 5 patients had undergone 3 operations prior to coming to the clinic. Most of these recurrent varicosities had been treated by repeated, massive courses of sclerosing agents following

TABLE I.—DISTRIBUTION OF EXTREMITIES

Year	Saphenous system involved	
	Greater	Lesser
1950	82	1
1951	102	5
1952	97	4
1953	112	5
1954	95	7
Total	488 (96 per cent)	22 (4 per cent)

the original ligation, but the effect of such treatment had been of relatively short duration. Of the 488 recurrences in the greater saphenous veins, 197 had been adequately ligated at the saphenofemoral juncture at the time of the original operation, and yet the superficial veins in the thigh and leg now demonstrated such marked incompetency that further sclerosing therapy was not advisable. Instead, the recurrent varicose veins were completely eradicated surgically.

It was observed that even after very extensive and repeated courses of sclerosing therapy had been given, it had been just a matter of a relatively short time, varying from a few months to a few years, before the superficial veins had recanalized and had become wide open again. The main saphenous channel was found to be recanalized up to the upper third of the thigh or even higher in all cases. Our clinical observations indicated that recanalization began distally and moved progressively in an upward direction when the ligation at the saphenofemoral juncture had been satisfactorily done. However, when ligation above had been done inadequately, recanalization also occurred from the groin downward as well as from the foot upward. Collateral veins and parallel tributaries were present in the thigh and leg in all instances.

Several patients had undergone high-low ligations or multiple ligations in the groin and leg, but invariably the ligated vessel either had recanalized to create a new channel through the operative scar or had formed a by-pass of the site of ligation by means of dilated collateral veins.

In this group of 197 extremities in which varicose veins had recurred after adequate ligation above, the medial femoral cutaneous tributary very frequently had not been ligated and now served as a most useful collateral channel, keeping the saphenous vein open up to the point of their union in the upper one-third of the thigh.

In the group of extremities in which the ligations above had been inadequate, a collateral hookup between a tributary of the saphenous stump above and the saphenous vein in the thigh below was frequently found. A common hookup involved the lateral superficial femoral cutaneous tributary above and the saphenous vein in the middle or lower third of the thigh. Another common hookup involved the labial vein above and the medial femoral cutaneous tributary of the greater saphenous vein below, over the inner aspect of the upper third of the thigh. Still another common collateral hookup involved an accessory saphenous vein above and superficial veins below, over the anterior and lateral aspects of the knee and leg. These hookups are illustrated in Figures 1 and 3.

Incompetent perforators. In accordance with the observations made by Luke, incompetent perforators played a very important role in the mechanism behind recurrence of varicose veins in a number of patients. Because of their direct connection with the deep veins, perforators had not been effectively controlled with sclerosing therapy. They were particularly prevalent when deep chronic venous insufficiency of long duration was present, and undoubtedly many competent communicating veins thus had been broken down by the increased ambulatory venous back-pressure over the years. Their importance in the "blow-out syndrome" has been well pointed out by Cockett and Jones. In our series of recurrent varicose veins, deep chronic venous insufficiency was diagnosed clinically in 93 lower extremities (18.2 per cent).

During recent years we have been more conscious of the importance of perforators and, therefore, have made a special effort to locate them before operation and to eliminate them at the time of operation. We be-

lieve that their true incidence is considerably higher than is indicated in our results. In our earlier cases, we often did not specifically mention or enumerate them in our operative notes. Furthermore, with accumulated experience, in recent years we are finding and eradicating many more perforators than we did in our earlier operations.

Inadequate ligation above. As suggested by Homans in 1916, it is essential in the surgical treatment of varicose veins that the saphenofemoral juncture be adequately ligated after all the tributaries have been dissected widely and ligated individually. Failure to do so invites early recurrence, as shown by Foote. An effective collateral hookup between the tributaries from the saphenofemoral juncture above and the superficial veins below, in the thigh and leg, develops quickly after inadequate ligation. An instance of this is illustrated in Figure 1.

We classified a ligation as inadequate if we found a remaining saphenous stump above with attached tributaries on re-exploration of the groin. Of the 488 ligations in the groin in this series, 291 (60 per cent) had not been adequately performed at the original operation. Our practice is to re-explore the groin in patients who have recurrence of the greater saphenous vein.

Of the 291 inadequate ligations in the groin, 40 were inadequate because the greater saphenous vein itself was not ligated, and 20 were inadequate because of the persistence of an accessory saphenous vein as the chief mechanism for recurrence. The last-mentioned vein, which is an important one, may have been overlooked at the original operation because of its more lateral position or it may have been mistaken for the femoral vein even though it is superficial to the deep fascia. Too small an incision for proper exposure is the most likely reason for error. It is obvious that an adequate exposure as well as a familiar knowledge of the anatomy of the groin is necessary. The remaining 231 inadequate ligations in the groin were inadequate because of the presence of saphenous stumps which varied from 2 to 10 centimeters in length and to which remaining tributaries were attached. A failure to ligate flush at the saphenofemoral juncture at the original operation was evident. The common errors found in the group of inadequate ligations are illustrated in Figure 2.

TABLE II.—SURGICAL FINDINGS ON RE-EXPLORATION OF THE GROIN IN 488 EXTREMITIES

Surgical findings	*Extremities*		
		No.	*Per cent*
Adequate ligation		197	40
Inadequate ligation		291	60
Ligation too low	231	48	
Ligation not done	40	8	
Accessory saphenous vein	20	4	

In many instances, even when the original ligations had been done adequately, the gap left from resection of the saphenous vein had become bridged by new, tortuous, small vessels that passed directly through the dense scar tissue from the proximal end of the greater saphenous channel below to the femoral vein above in the region of the fossa ovalis. This evidence indicates that leaving the greater saphenous channel in the thigh permits re-establishment of a hookup.

Of the 22 lesser saphenous veins reoperated on by us, none had been ligated adequately at the saphenopopliteal juncture. Although tributaries are not as numerous here as in the groin, there is still definite danger of collateral hookups unless an adequate ligation close to the popliteal vein is performed.

Our findings indicate that one of the essentials of proper surgical treatment of varicose veins, namely adequate ligation above, had been neglected in the majority of cases of recurrent varicose veins comprising this study.

IMPORTANCE OF CORRECT DIAGNOSIS

It is essential that incompetency of the saphenous system be correctly diagnosed prior to operation so that it will not be overlooked and left behind at operation, and hence will not require that another operation be performed at a later date. Con-

FIG. 1.

FIG. 1. Collateral hookup between labial vein and tributary of greater saphenous vein on right, and between accessory saphenous vein and tributaries over anterior part of knee on left. Bilateral incomplete stripping had been done elsewhere 5 years previously.

FIG. 2. Findings on re-exploration of groin (based on 488 extremities). a, Ligation too low: 48 per cent of extremities. b, Persistent greater saphenous vein: 8 per cent. c, Persistent accessory saphenous vein: 4 per cent. d, Adequate ligation above: 40 per cent.

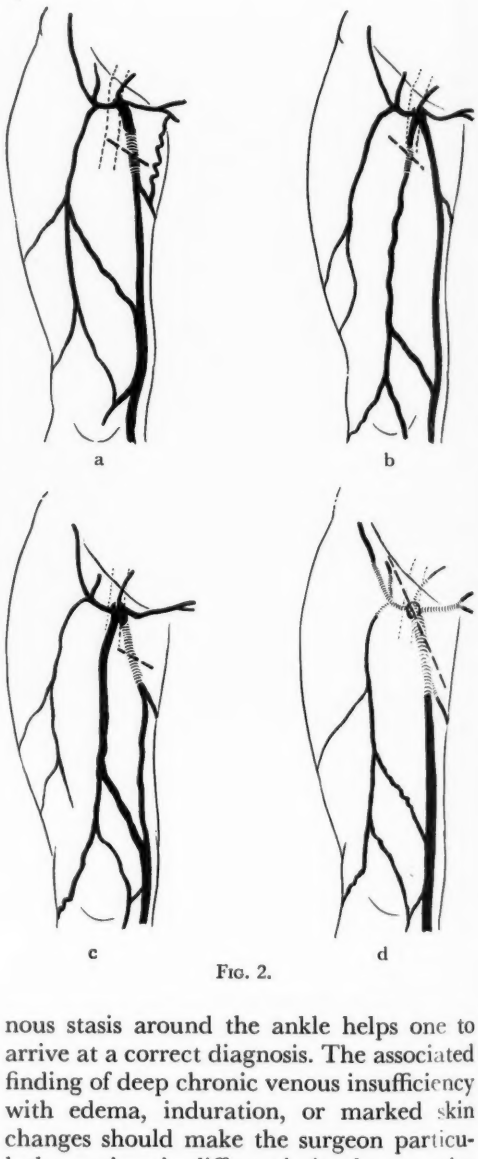

FIG. 2.

versely, it is important not to remove a competent saphenous system, as this definitely would not improve the overall venous function in the lower extremity.

The diagnosis of recurrence of varicose veins is based on the history, inspection, and examination. Inspection plays a vital role in making the diagnosis. The presence of large varicose veins and their association with scars that are too low in the groin are evidence of recurrence of veins. The finding of incompetent perforators or tortuous segmental veins that lead into the area of venous stasis around the ankle helps one to arrive at a correct diagnosis. The associated finding of deep chronic venous insufficiency with edema, induration, or marked skin changes should make the surgeon particularly cautious in differentiating between incompetent superficial veins and competent dilated collateral veins. The former should be removed to lessen the venous stasis in the leg and to improve overall venous function, while the latter should be left alone.

In the examination of the leg, perforators and their associated fascial defects are care-

fully palpated by the examiner's fingers while the patient stands on the table under good illumination. We have found that 2 simple clinical tests, namely the compression test and the retrograde filling test, are sufficient. The palpation test of Schwartz-Heyerdale, as modified by Myers into a compression test, is very useful, provided the lumen of the vein is wide open and the wall is not too thick and scarred. In recurrent varicose veins, the wall of the vein is often not normal or resilient because of previous sclerosing therapy, and therefore impacts are sometimes not freely transmitted along the course of such veins. When the impact is transmitted freely to a point within or above the scarred area of the groin, it indicates a wide-open saphenous channel as seen in persistent saphenous veins and in massive collateral hookups. The compression test is useful in most cases of recurrent varicose veins, though in a small but definite group the test is not effective due to thickness of the wall of the veins.

The retrograde filling test, originally the Brodie-Trendelenburg test, gives prima facie evidence of incompetency. Again, this test depends on an open lumen and on resilient and expansible walls that readily demonstrate back-filling on release of the tourniquet above. It may not be helpful when extensively scarred veins are present, as sometimes seen in recurrent varicosities.

ESSENTIALS OF ADEQUATE SURGICAL TREATMENT

Complete removal of all incompetent superficial veins is the goal to be achieved in the surgical treatment of varicose veins. The essentials of such treatment, as stressed by Myers (6, 7), include therefore (1) adequate ligation above at the saphenofemoral or the saphenopopliteal juncture, (2) thorough removal of all incompetent superficial veins below, down to the dorsum or lateral aspects of the foot, by stripping and dissection, and (3) resection and ligation of all incompetent perforators in the thigh, leg, and foot.

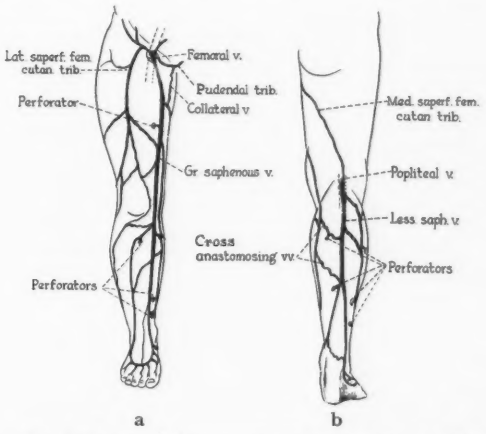

FIG. 3. Pattern of recurrent varicose veins. a, After ligation in groin. b, After ligation behind knee.

The pattern of superficial veins is never the same from one patient to the next, and therefore each operation is an individual anatomic problem that has to be solved by the surgeon. Figure 3 illustrates patterns of recurrent varicose veins seen after ligation in the groin or behind the knee, and demonstrates many of the incompetent superficial veins and perforators that may have to be eradicated.

Our practice in the treatment of recurrent varicose veins is to perform an operation that will remove all varicose veins as completely as if the patient had never had previous surgical treatment of the veins. In recurrence of greater saphenous veins, the groin is always re-explored, even though this may at times be difficult because of the extensive scarring from previous operative procedures. A long diagonal incision is necessary for adequate exposure. If the previous ligation has been too low, easy exposure is obtained by dissecting into the saphenofemoral region from above to expose the neck of the saphenous stump. After the neck has been ligated flush with the femoral vein, the stump can be resected and removed in a retrograde fashion in a manner that prevents troublesome bleeding and possible injury to the femoral vessels. All tributaries attached to the saphenous stump are dis-

sected out widely and ligated individually. If the previous ligation has been high and there is no long saphenous stump, it may be necessary to approach the saphenofemoral juncture from below or from the side and through the scar tissue already present. The surgeon must be sure that there are no remaining tributaries attached to the saphenofemoral juncture before he proceeds with removal of the superficial veins below.

If the proximal end of the greater saphenous vein in the lower portion of the groin cannot be located promptly with limited exploration, the passing of an intraluminal stripper from below upward is very helpful in locating quickly the saphenous trunk. The medial femoral cutaneous tributary, which is found constantly, is ligated and resected where it joins the greater saphenous vein in the lowermost portion of the incision in the groin. The greater saphenous vein is removed throughout its extent from the dorsum of the foot to the groin, as are all superficial parallel veins or tributaries coursing down the thigh and leg. Often many of these veins are scarred and are very adherent to surrounding tissue because of previous sclerosing therapy. If the lumen of the vein does not permit the passage of a flexible intraluminal stripper, an extraluminal stripper may have to be employed. At times the surgeon has to resort to direct dissection. All superficial plexuses of veins in the thigh or leg and all large cross-anastomosing veins between the greater and the lesser saphenous systems must be removed.

In the treatment of recurrent varicosities of the lesser saphenous vein, a transverse incision is made approximately 2 to 3 centimeters above the popliteal fold, the popliteal fascia is divided into a longitudinal direction, and the ligation is made flush with the popliteal vein after all encountered tributaries have been tied off.

Incompetent perforators are given special attention. They may be encountered anywhere around the ankle, leg, or thigh, though a characteristic pattern is usually the rule, as has been well pointed out by Sherman. The most frequent site is over the inner aspect of the distal third of the leg. In recurrent varicosities, they play a most important role because they stubbornly resist sclerosing therapy on account of their direct close association with the deep veins. They are often associated with stasis changes above the inner aspect of the ankle. When deep chronic venous insufficiency is present, perforators are most prevalent and demand close attention by the surgeon. In removal, they are followed down to a level beneath the deep fascial layer where they are individually resected and ligated.

Preoperatively, all incompetent superficial veins and perforators are traced and mapped out by the examiner's fingers while the patient stands at rest on the table. All veins are marked with an indelible dye solution (pyrogallic acid formula[1]) so that they can readily be found at operation.

Postoperatively, sclerosing therapy is used for any small superficial veins that may remain. The amount of sclerosing solution required is a rough index of the completeness of surgical eradication of the veins. Thus, of 147 patients who underwent 219 surgical procedures for recurrent varicose veins during the last 2 years of this study, 49 per cent required no sclerosing therapy during the immediate postoperative period, while 51 per cent required an average dose of 3.5 cubic centimeters of sclerosing solution.

A return to normal physiologic range of venous function following surgical treatment was demonstrated by measurement of ambulatory venous pressure before and after stripping 13 recurrent incompetent greater saphenous veins in this series (4).

COMMENT

From a review of the present series of recurrent varicose veins, it is evident that it is just a matter of time before nature recanalizes and opens up all superficial veins that are left behind to be temporarily oc-

[1]Pyrogallic acid, 5 grams; acetone, 50 cubic centimeters; solution of ferric chloride N. F., 40 cubic centimeters; and ethyl alcohol to make 100 cubic centimeters. Put in dark bottle, do not expose to air excessively. Remake every 10 days.

cluded by injection therapy during or shortly after the operation of ligation only. For this reason, we firmly believe that the best countermeasure against possible future recurrence is thorough surgical eradication of all incompetent veins in the thigh, leg, and foot. Since varicose veins constitute a chronic affliction with a slow but progressive breakdown of all veins in a susceptible individual, the nature of the condition itself prohibits the surgeon from making a positive prediction about a permanent surgical cure. He can successfully arrest this progressive condition for an indeterminate period, and this period is increased when the veins are thoroughly removed surgically.

Adequate high ligations followed by sclerosing therapy were performed for varicose veins in 111 lower extremities by competent surgeons at the clinic prior to 1947, yet in all instances there was extensive recurrence of the varicosities within a few years. Comparative results between the high ligation-injection operation and the stripping operation are difficult to determine accurately in numerical percentages, but the recurrence rate with the former surgical procedure has remained inordinately high. A comparative study between partial and complete stripping operations at the clinic, reported by Myers and Smith, bears out the thesis that complete surgical removal of all incompetent superficial veins offers the patient the best prognosis in the long run. The need for periodic follow-up examination at least every other year cannot be overemphasized in the treatment of a condition to which the patient already has demonstrated a marked susceptibility.

Our study indicates that the mechanism behind recurrence of varicose veins was associated with inadequate ligation at the saphenofemoral or saphenopopliteal junctures in 61 per cent of all extremities; some of these recurrences might have been prevented by adequate ligation alone. In the remaining 39 per cent of the extremities, in spite of adequate ligation above, recanalization and breakdown of all superficial veins and perforators had occurred from nature's continuous effort, and this was the chief mechanism for recurrence. Therefore, we are convinced that the best method to prevent recurrence of varicose veins must include not only adequate ligation above but also thorough surgical eradication of all incompetent superficial veins and perforators below in the thigh, leg, and foot. The optimal time to prevent recurrent varicose veins is during the original operation.

SUMMARY AND CONCLUSIONS

Of 510 surgical procedures performed on 341 patients during a 5 year period for so-called recurrent varicose veins, 96 per cent were done because of recurrent varicosities of the greater saphenous veins, and 4 per cent were done because of recurrent varicosities of the lesser saphenous veins. Whereas the ligations had been inadequate in 61 per cent of the 510 extremities and adequate in 39 per cent, there remained incompetent superficial veins in the thigh, leg, and foot in *all* instances and incompetent perforators in many cases.

On the basis of this study it is pointed out that the essentials of adequate surgical treatment of varicose veins include: (1) adequate ligation above at the saphenofemoral or saphenopopliteal junctures, (2) thorough removal of all incompetent superficial veins below, down to the dorsum, or lateral aspects of the foot, by stripping and dissection, and (3) individual ligation and resection of all incompetent perforators present.

Thorough eradication of all the incompetent veins is the most effective preventive measure against recurrence. To ensure that a satisfactory result is maintained, periodic follow-up examinations are necessary.

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OBSERVATIONS ON PATIENT TOLERANCE WITH INTRAVENOUS ADMINISTRATION OF FAT EMULSION

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THE PROBLEM OF MAINTAINING ADEQUATE NUTRITION by intravenous alimentation has been hampered by the inability to supply conveniently an adequate number of calories. Dextrose, invert sugar, fructose, alcohol, and protein hydrolysates have been utilized for this purpose and have been found calorically inadequate within the practicable limits of use. In 1935, Holt and associates, following the lead of earlier investigators, made the first practical attempt in this country to provide intravenous calories by the administration of fat emulsion. Since that time and particularly within the last decade, the need for an emulsion of fat with its high caloric potentiality has been emphasized by the intense efforts to provide such a solution which would be safe, effective, and otherwise appropriate for intravenous use. Regardless of their composition, administrations of improved fat emulsions have been attended by a variety of undesirable side effects. Failure to understand the etiology and significance of these reactions has prevented the acceptance of fat emulsion as a means of supplying intravenous calories.

The purpose of our work has been the evaluation of a new fat emulsion as an available source of intravenous calories. So far as can be determined, our experience with more than 1,000 administrations in over 300 patients is one in which the largest group of infusions of a fat emulsion of uniform composition has been employed. Based upon the results of the first 633 administrations in 209 patients, this report is a presentation of: (1) the character and incidence of reactions, (2) the effect of variables on the incidence of reactions, and (3) the estimated calories lost by postinfusion temperature rises. This additional clinical experience may help to delineate type, incidence, and importance of various reactions and to justify the use of presently available fat emulsion when adequate intravenous calories are paramount to the patient's well-being.

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MATERIALS AND METHODS

Fat emulsion. Each of the 15 lots of fat emulsion used contained 10 per cent (wt./vol.) sesame oil, U.S.P., 4.5 per cent (wt./vol.) dextrose, U.S.P., and 0.65 per cent (wt./vol.) soybean phosphatides. The emulsion was homogenized under high pressure, collected in vacuum bottles, and sterilized by autoclaving. Before its release, each lot was subjected to extensive testing by the manufacturer to meet rigid specifications pertaining to composition, particle size, sterility, thermogenicity, toxicity, antigenicity, vasomotor activity, and compatibility with human plasma. Age of the emulsion at the time of administration varied from 1 to 5.2 months.

Selection of patients. A majority of the 209 adult male patients were infused because of their need for supplemental caloric intake, either because of chronic malnutrition or because of inadequate postoperative nutrition. The remaining patients, hospitalized for minor surgical procedures, were volunteers who did not represent nutritional

TABLE I.—633 INTRAVENOUS ADMINISTRATIONS OF FAT EMULSION TO 209 PATIENTS

Volume per administration, milliliters	*Administrations per patient*	*No. of patients*	*No. of administrations*	*Liters per patient*	*Total volume in liters*	*Liters per administration*
350	1	14	14	0.2	2.8	
	2	5	10	0.4	2.0	
500	1	55	55	0.5	27.5	
	2	16	32	1	32	
	3–8	9	35	1.7	12.5	
1,000	1	31	31	1	31	
	2	48	96	2	96	
	3	24	72	3	72	
	4	11	44	4	44	
	5–10	7	45	6.4	45	
1,500	1	25	25	1.5	37.5	
	2	18	36	3	54	
	3	8	24	4.5	36	
	4	10	40	6	60	
	5–7	11	62	8.4	93	
2,000	1	1	1	2	2	
	3	2	6	6	12	
	5	1	5	10	10	
Means and totals	3	209	633	3.2	668.5	1.05

problems. In the 209 patients studied, 53 diagnoses were made. They represented a diversified group of neoplasms, inflammatory disease of the gastrointestinal tract, fractures, burns, cirrhosis, pancreatitis, and atherosclerosis. Since no disease entity was intentionally excluded, the observations made reflect the incidence and type of side effects that may be expected with the general use of intravenous fat emulsion.

Method of administration. In general, each patient received an initial test infusion of 500 milliliters. If toleration was satisfactory, the infusion was continued to a total of 1,000 milliliters. If the patient reacted unfavorably, the infusion was discontinued and repeated on a second day. If the patient's response was unfavorable on the second day, no further administrations were attempted. Rate of administration averaged 235 milliliters (23.5 grams of fat) per hour for 4 hours but was varied according to the patient's tolerance. The maximum rate was 400 milliliters (40 grams) per hour for 5 hours. These dose rates approach, and in some instances exceed, the 20 grams per hour for 6 hours which Kinsell has reported exceeds tolerance. Temperature, pulse, respirations, and blood pressure were recorded before, during, immediately after, and 2, 6, and 20 hours after infusions. All other objective data and subjective complaints that occurred during the infusions and for several hours afterward were recorded.

TABLE II.—PRINCIPAL REACTIONS NECESSITATING TERMINATION OF INFUSIONS

Volume of infusion	*Chest pain*	*Dyspnea*	*Chill*	*Nausea or vomiting*	*Rash*	*Arthralgia*	*Infusions discontinued*
0–100 ml.		2	4	1	1	1	9
100 to 250 ml.			14	1			15
250 to 500 ml.			7				7
500 to 1,000 ml.			3	2			5
1,000 to 1,500 ml.	1		1				2
Total	1	2	29	4	1	1	38

Number of administrations. The data on the administration of fat emulsion are given in Table I. The greatest volume of fat emulsion administered at one infusion was 2,000 milliliters. The mean volume per administration was 1,050 milliliters, and each patient received a mean total volume of 3,200 milliliters.

RESULTS

Side effects. Excluding temperature changes which will be considered separately, 62 per

cent of all infusions were without any untoward effects, while 6 per cent of infusions were discontinued because of undesirable reactions (Table II). The side effects fell into three groups with respect to time of onset. Back pain, flushing, chest pain, and dyspnea, if observed, usually occurred after administration of a few drops or milliliters of emulsion. Chills and associated pyrexia did not occur before the administration of 100 to 300 milliliters of emulsion. Headache, nausea, vomiting, arthralgia, and blurring of vision rarely occurred before 500 milliliters were administered.

Back pain (incidence, 10.8 per cent[1]) usually started after the administration of the first few milliliters of emulsion, although the onset sometimes began later in association with chill. The pain was sudden, often severe and intense, but of short duration. If it persisted longer than a few minutes, its character changed to a dull, annoying ache. The pain was most often referred to the lumbar or sacral spine and less frequently to the dorsal or cervical spine. It occasionally radiated to the legs, groin, perineum, or abdomen. Infusions were discontinued at the onset of pain, but were resumed prior to its complete disappearance because experience showed that pain would not recur. Twenty milligrams of benadryl were used intravenously in many patients at the onset of back pain. Because of the short duration and ill defined termination of this reaction, it was difficult to arrive at an accurate appraisal of the usefulness of this drug. It was our opinion, however, that benadryl was helpful in alleviating back pain.

Flushing (incidence, 6.8 per cent) of the face, neck, and chest, frequently a forerunner of back pain, usually occurred early, but occasionally its first appearance was associated with a chill. The reaction was usually mild, transitory, and unknown to the patient, but occasionally it was intense, vivid, and associated with a surging, burning sensation in the chest, extending into the neck. Although flushing was of short duration, it appeared to be diminished by antihistaminics.

[1]Based on total number of administrations.

TABLE III.—MAXIMUM ALTERATIONS IN PULSE RATE

Maximum change in pulse rate per min.		*Per cent of total No. of infusions*
−50	−41	0.2
−40	−21	1.4
−20	0	26.6
0	20	57.5
21	40	12.5
41	60	1.4
61	80	0.2

TABLE IV.—COMPARISON OF MAXIMUM ALTERATIONS IN PULSE RATE IN 3 GROUPS OF INFUSIONS

	All infusions	*56 infusions associated with chill*	*38 infusions discontinued because of reactions*
Range	+80 −50	+60 −28	+50 −28
Mean	+7	+12	+17
Per cent of infusions with change in pulse rate >+20	14.1	25.0	40.0
Per cent of infusions with change in pulse rate >−20	1.6	5.7	5.7

Chest pain (incidence, 2.4 per cent), compressive and smothering in character, was usually accompanied by one or more of the following: chill, back pain, flushing, dyspnea, apprehension, and a varying degree of cyanosis. Prompt relief from pain resulted from temporary discontinuance of infusion and intravenous administration of benadryl. Electrocardiograms recorded during the occurrence of chest pain revealed no acute changes; these records, however, were made with insufficient frequency to draw conclusions.

Dyspnea (incidence, 4.4 per cent), with or without chest pain or cyanosis, occurred at the beginning of infusion or at the time of chill. Except for dyspnea associated with

TABLE V.—MAXIMUM ALTERATIONS IN BLOOD PRESSURE

Maximum blood pressure change, mm. of mercury		*Per cent of total No. of infusions*	
		Systolic	*Diastolic*
−50	−41	0.4	0.6
−40	−21	2.9	4.1
−20	0	20.3	25.0
0	20	54.0	59.0
21	40	17.0	10.4
41	60	5.0	0.6
61	80	0.2	0
81	90	0.2	0

TABLE VI.—COMPARISON OF MAXIMUM ALTERATIONS IN BLOOD PRESSURE IN 3 GROUPS OF INFUSIONS

	All infusions		*56 infusions associated with chill*		*38 infusions discontinued because of reactions*	
	Systolic	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*
Range	+88 −40	+40 −44	+88 −40	+34 −28	+88 −35	+40 −44
Mean	−	−	+11	+4.4	+15	+7.6
Per cent of infusions with change in blood pressure > +20	22.4	11.0	26.5	18.0	38.0	21.0
Per cent of infusions with change in blood pressure > −20	3.3	4.7	5.8	3.0	5.8	10.0

severe chills, patients with this reaction usually responded with remarkable improvement to intravenous benadryl. As a rule, dyspnea occurring at the beginning of an infusion did not occur with subsequent infusions.

Chills (incidence, 8.9 per cent) usually occurred suddenly, without warning, and subsided within 15 to 30 minutes if the infusion was temporarily discontinued. If there were no other reactions or subjective complaints, the administration was resumed at a slow, but increasing, rate. Further chills rarely occurred even when the normal rate was reached and maintained. Patients with chills usually, but not always, developed a rise in temperature, and it was not uncommon for chills to be associated with nausea, vomiting, severe headache, back pain, flushing, dyspnea, cyanosis, or a general feeling of ill-being. The temperature remained at an elevated plateau, but occasionally declined during completion of infusion. Severe chills and associated side effects accounted for 29 of the 38 infusions discontinued because of the reactions.

Headache (incidence, 10.4 per cent), occasionally observed by patients receiving small amounts of emulsion, was most likely to occur after a large infusion. While intensity of headaches varied greatly, their location was predominantly frontal or postorbital. Headaches were not associated with hypertension, and empirin or aspirin relieved most, although others persisted for as long as 12 hours.

Nausea and vomiting (incidence, 12.0 per cent) were most commonly associated with large infusions or infusions complicated by chills. Anorexia was not considered a reaction but was sometimes associated with large infusions. It seldom persisted for more than 1 meal, except when nausea or vomiting was present, and then it was likely to be prolonged for 2 meals.

Arthralgia (incidence, 1.6 per cent) was associated with large infusions. The patients complained of feeling "achy all over, as if they had the 'flu'." This reaction which usually persisted throughout the day and most of the night was most severe in a patient with rheumatoid arthritis in remission. He complained of generalized arthritic pains, similar to those experienced with his illness.

Dizziness or syncope (incidence, 3.5 per cent) was attributed to patients ambulating immediately after completion of a large infusion. Because of this experience, it is now the practice to keep patients in bed for 30 to 60 minutes after infusion.

Rashes (incidence, 2.1 per cent) were of 2 types. The first, occurring after a small volume of fat emulsion, consisted of generalized urticarial wheals which usually disappeared promptly after antihistaminics. The second, occurring after several large infusions of fat emulsion, consisted of a maculopapular eruption, most pronounced over the hands, arms, and chest. The latter type was not influenced by antihistaminics and persisted for several days without causing the patient discomfort, except for occasional mild pruritus.

TABLE VII.—MAXIMUM TEMPERATURE RESPONSES TO INTRAVENOUS ADMINISTRATION OF FAT EMULSION

Temperature (°F)	*No. of infusions*	*Per cent of total No. of infusions*
97–98.9	189	29.8
99–99.9	221	35.0
100–100.9	148	23.5
101–101.9	53	8.4
102–102.9	19	2.9
103 or >	3	0.5

TABLE VIII.—FREQUENCY OF REACTIONS ASSOCIATED WITH INFUSIONS MADE CONSECUTIVELY

	Infusions							
	1	*2*	*3*	*4*	*5*	*6*	*7 to 10*	*Total*
No. of infusions	209	161	102	74	28	24	35	633
Back pain	46	14	4	4	0	0	0	68
Chest pain	8	4	1	1	1	0	0	15
Flushing	31	6	4	1	0	1	0	43
Dyspnea	18	6	0	0	2	2	0	28
Chill	35	14	3	1	0	2	1	56
Nausea or vomiting	26	27	6	7	4	4	2	76
Eye complaint	3	4	4	2	1	1	2	17
Headache	29	19	6	7	2	2	1	66
Rash	4	2	3	2	0	2	0	13
Sweating	13	3	3	1	0	1	0	21
Dizziness	7	6	4	3	0	0	2	22
Arthralgia	7	2	1	0	0	0	0	10
Diarrhea	0	3	1	2	0	1	0	7
Bleeding	1	1	2	1	1	0	0	6
No. of infusions without reactions	94	97	76	54	23	21	29	394
Per cent of infusions without reactions	45	60	75	73	82	87	83	62

Blurring of vision (incidence, 2.5 per cent) was associated with large infusions. This response was similar to that observed by patients on large doses of anticholinergic drugs. No abnormality was noted on funduscopic examination, and the effect subsided without medication a few hours after termination of infusion.

Miscellaneous reactions, such as vague abdominal discomfort, fullness, gas pains, or cramps, were reported infrequently. These complaints were not severe, and no significance was attached to them. Evidence of bleeding was associated with the use of fat emulsion 6 times in 5 patients. One patient developed minimal hemoptysis after 2 infusions of 1,000 milliliters. Epistaxis occurred 4 times in 3 patients. In the first patient, it occurred at the conclusion of the second infusion of 1,000 milliliters; in the second, at the end of the third infusion of 1,000 milliliters; and in the third, after the fourth and fifth infusions of 2,000 milliliters. One patient with a diagnosis of cirrhosis received 600 milliliters of emulsion and developed bleeding from the gums. All instances of bleeding stopped spontaneously. Diaphoresis, accompanied by no other untoward reaction, diarrhea, associated with large infusions, and excessive lacrimation were infrequent reactions. A peculiar metallic taste was noted by some patients almost simultaneously with the beginning of infusion. This subjective response was of short duration and was always associated with other reactions known to occur at the onset of an infusion.

Cellulitis, occurring at the infusion site, was primarily the result of accidental subcutaneous infiltration of emulsion. Although the arms were frequently red, hot, and tender, no sloughs developed. One patient who accidentally received 400 milliliters of emulsion subcutaneously in the axilla was an exception, since the emulsion was promptly absorbed, and at no time did the patient complain of pain or soreness. The severity of cellulitis resulting from infiltration was minimized when moist heat was applied as soon as the accident occurred. Multiple infusions into an extremity were frequently associated with venous thrombosis and low grade inflammation in the absence of subcutaneous infiltration.

Maximum changes in pulse rate due to infusion of fat emulsion are tabulated in Table III. In Table IV, a comparison is made between the pulse rate changes occurring during all infusions, those occurring in the group of 56 infusions producing chills, and those occurring in the group of 38 infusions discontinued because of reactions. In the latter 2 groups, the pulse rate change was greater than $\pm$ 20 beats per minute, 2 to 3 times as often as in the total group; the range and overlap between the 3 groups, however, were too great to assign prognostic significance to pulse changes.

TABLE IX.—FREQUENCY OF REACTIONS ASSOCIATED WITH ADMINISTRATION OF DIFFERENT VOLUMES

	Volume of infusions					
	350 ml. or less	*500 ml.*	*1,000 ml.*	*1,500 ml.*	*2,000 ml.*	*Total*
No. of infusions	24	122	288	187	12	633
Back pain	8	20	32	8	0	68
Chest pain	2	1	8	4	0	15
Flushing	14	11	16	2	0	43
Dyspnea	8	5	10	5	0	28
Chill	23	11	20	2	0	56
Nausea or vomiting	13	6	31	25	1	76
Eye complaints	0	2	7	8	0	17
Headache	8	9	24	22	3	66
Rash	4	1	3	4	1	13
Sweating	7	6	6	2	0	21
Dizziness	0	4	10	8	0	22
Arthralgia	1	0	6	3	0	10
Diarrhea	0	0	2	4	1	7
Bleeding	0	1	2	1	2	6
No. of infusions without reactions	1	82	166	136	9	394
Per cent of infusions without reactions	4.1	67	57	73	75	62

TABLE X.—REACTIONS OBSERVED WITH 44 INFUSIONS TO 22 PATIENTS WITH HEPATIC DISEASE

	Volume of infusions			
	0 to 350 ml.	*350 to 500 ml.*	*500 to 1000 ml.*	*Total*
No. of infusions	7	6	31	44
Back pain	2	4	7	13
Chest pain	2	0	2	4
Flushing	2	2	3	7
Dyspnea	2	1	1	4
Chill	6	3	9	18
Nausea or vomiting	2	4	10	16
Eye complaint	1	1	1	3
Headache	2	2	7	11
Rash	0	1	1	2
Sweating	3	0	2	5
Dizziness	1	1	3	5
Arthralgia	0	0	1	1
Diarrhea	0	0	0	0
Bleeding	0	1	2	3
No. of infusions without reactions	0	0	11	11
Per cent of infusions without reactions	0	0	35.5	25

Maximum alterations in blood pressure due to fat emulsion are tabulated in Table V. The systolic pressure was elevated in 76 per cent of the infusions and the diastolic in 70 per cent. In Table VI, the total number of infusions with blood pressure changes greater than ± 20 millimeters of mercury is compared with similar figures for the 56 infusions producing chills and the 38 infusions discontinued because of reactions. While there was a decided increase in the relative incidence of elevated blood pressure in the latter 2 groups, the difference was found to be of no significance as a reliable prognostic sign.

Approximately 70 per cent of all administrations of fat emulsion were accompanied by an elevation in the patient's temperature (Table VII). Included in this tabulation are the data from 32 administrations in which the initial temperature was above 100 degrees Fahrenheit. The duration of temperature elevation was directly related to the volume of emulsion received. Since infusions were begun early in the morning, preinfusion temperatures were often 1 to 1.5 degrees Fahrenheit below "normal." For this reason, the highest temperature recorded for the 24 hour period following the start of infusion, rather than the

number of degrees rise above the preinfusion level, was considered the maximum temperature response.

About 3 per cent of the infusions resulted in temperature elevations above 102 degrees Fahrenheit, and 12 per cent of the infusions caused temperatures above 101 degrees Fahrenheit. In 65 per cent of the administrations, the maximum temperature was below 100 degrees Fahrenheit.

There were no noteworthy changes in the respiratory rate.

Effect of variables on incidence of reactions. Critical examination of our results did not reveal a significant difference in the incidence of reactions accompanying different lots. Storage of fat emulsion at room temperature for 5 months did not affect the incidence of either early or late reactions.

Alteration in reaction rate for consecutive infusions of intravenous fat emulsion is tabulated in Table VIII. Between the first and second administrations, infusions without reactions increased from 45 per cent to 60 per cent, while the average number of reactions per administration decreased from 1.09 to 0.69. Improvement in the reaction rate noted in Table VIII after second infusions was the result of selection of cases and did not represent a further increase in tolerance with succeeding administrations. Of the 209 patients studied, 48 received fat only once; 21 had reactions, and 27 did not. If the remaining 161 patients who had 2 infusions are considered, the incidence of infusions without reactions increased from 40 to 60 per cent between the first and second administrations. This increase in tolerance is significant ($p < 0.01$).

The incidence of reactions which occurred with infusions of different volumes of fat emulsion are given in Table IX. All but 1 infusion of less than 500 milliliters were discontinued because of reactions; therefore, the highest incidence of reactions occurred with infusions of this group. The reaction rate decreased for infusions of 500 milliliters, but again increased for infusions of 1,000 milliliters when reactions common to larger volumes appeared. Patients receiving more than 1,000 milliliters of fat emulsion were selected because of their tolerance, thus accounting for the lower reaction rate in this group.

TABLE XI.—MAXIMUM TEMPERATURE RESPONSE OBSERVED WITH 44 INFUSIONS TO 22 PATIENTS WITH HEPATIC DISEASE

Temperature (°F)	*No. of infusions*	*Per cent of total No. of infusions*
97–98.9	6	13.6
99–99.9	6	13.6
100–100.9	13	29.5
101–101.9	11	25.0
102–102.9	8	18.2

Fat emulsion was administered 44 times to 22 patients with hepatic disease. This group received 7 per cent of all infusions and contributed 12 (31 per cent) of the 38 infusions discontinued because of reactions. Only 11 (25 per cent) of these infusions were without reactions (Table X), and 9 of these were in cases with a total serum bilirubin greater than 4.0 milligrams per cent. The thermogenic response to fat emulsion in patients with hepatic disease was also greater than that in the overall group of patients (Table XI). The temperature rose above 100 degrees Fahrenheit in 73 per cent of the infusions made in these cases as compared with a similar rise in 35 per cent of the total group. This difference is significant ($p < 0.01$).

The most serious reactions observed occurred during 2 infusions in a case of adrenal insufficiency in which the stomach and one adrenal gland had been surgically removed for gastric carcinoma and in which the other adrenal gland was demonstrated at subsequent postmortem examination to be replaced by carcinoma. Both infusions were terminated after 100 to 150 milliliters of emulsion because of the sudden onset of flush, chest pain, chills, dyspnea, and cyanosis which required the urgent administration of oxygen, aminophyllin, and cortisone.

Deaths. Three patients died within 24 hours of the administration of intravenous fat emulsion. The demise of 2 of these patients was attributable to their primary disease,

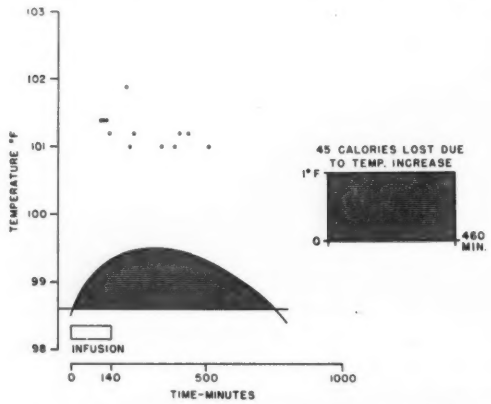

FIG. 1. The mean temperature elevation of 50 patients receiving 500 milliliter infusions (72 administrations) of fat emulsion was equivalent to a loss, as useless heat, of 8 per cent of the infused calories.

inoperable carcinoma of the pancreas and of the stomach, respectively, and was unrelated to the administration of fat. The third case involved a 67 year old neuropsychiatric patient with an old fracture of the hip treated without surgery. Prior to infusion, the blood pressure, temperature, pulse, and respiration were 155/95, 99.4 degrees Fahrenheit, 90, and 20, respectively. During the infusion, the patient became belligerent, but did not otherwise demonstrate any ill effects until after the administration of 480 milliliters of emulsion when the infusion was discontinued because of the sudden onset of diaphoresis. The blood pressure, temperature, pulse, and respiration were then 148/104, 99.2 degrees Fahrenheit, 84, and 16, respectively and remained unchanged for the next 5 hours. Diaphoresis ceased, and the patient appeared comfortable. Sixteen hours after the infusion, the patient died of a ruptured aneurysm of the left ventricle. Microscopic examination of the lung, liver, spleen, and kidney revealed no unusual accumulation of fat in these 3 patients.

Loss of infused calories. The first 250 infusions were grouped according to the volume of fat emulsion administered. The temperatures recorded prior to these infusions and, for the succeeding 24 hours, were used to construct mean temperature curves for infusions of 500, 1,000, and 1,500 milliliters (Figs. 1, 2, and 3). Assuming that the caloric expenditure resulting from a rise in temperature of 1 degree Fahrenheit for 24 hours was equivalent to 140 calories, the per cent of infused calories lost as useless heat following intravenous administration of fat emulsion was estimated from the mean temperature curves. This loss ranged from 8 per cent of the infused calories with administration of 500 milliliters of emulsion to 4 per cent with 1,000 and 1,500 milliliters. Such losses were considered unimportant.

DISCUSSION

There is substantial evidence that fat emulsion can provide a convenient and adequate source of intravenous calories. Acceptance of this form of parenteral therapy has been retarded by reactions of unknown etiology and significance associated with the introduction of one colloidal system, fat emulsion, into a more complex colloidal system, namely blood. Like Waddell and associates we have observed, in using intravenous fat, all of the reactions observed by Nissim following intravenous administration of colloidal iron. The nature of the colloidal reactions within the body is speculative. The possibility of histamine release causing early reactions and overloading of the reticuloendothelial system causing late reactions are presently under consideration. There is no evidence to support an anaphylactic response to fat emulsion as the cause for reactions.

Our experience with the intravenous use of a particular fat emulsion is similar to that of other investigators using emulsions of many different compositions. Sixty-two per cent of infusions were without reactions other than temperature changes. Thirty-eight per cent of infusions were complicated by reactions. Of these, it was considered medically prudent to discontinue 6 per cent, while the remaining 32 per cent were completed with consent of the patients.

We believe it is impossible to compare accurately the relative incidence of reactions reported by different investigators. Too much depends upon the definition of the word "reaction" and on the circumstances under which measurements are made and subjective complaints recorded. Certainly, no fat emulsion has been prepared and administered to a large number of patients with as few reactions as are caused by ordinary solutions used for intravenous nutrition. Indeed, there is some evidence that an emulsion with such a low incidence of reactions may be unobtainable. It is possible that reactions may be due, not to the composition and structure of the fat emulsion, but to the interaction of the emulsion with the patient's body in a particular physiochemical state which may vary from day to day. A large portion of our data indicates the likelihood of this possibility. Some patients tolerate large volumes of fat with no difficulty; some patients are completely intolerant; while others, who react unfavorably to the first infusion, may subsequently tolerate fat emulsion satisfactorily. This variation suggests that a patient's tolerance and ability to develop tolerance are due to differences within the patient as well as to the physical or chemical properties of the fat emulsion. Whether the variation in patient tolerance is the result of normal physiologic alterations or is secondary to disease is only speculative.

Holt and associates raised the possibility that intravenous administration of fat was contraindicated in children with hepatic disease. Shafiroff, on the other hand, stated that patients with cirrhosis tolerated fat satisfactorily. Our experience with fat emulsion demonstrated that the incidence of reactions was significantly greater in patients with hepatic dysfunction than in other patients. An exception to the high reaction rate in patients with liver disease occurred when the total serum bilirubin was greater than 4 milligrams per cent. The mechanism for the lack of tolerance in cases of hepatic disease is not clear. We did not observe, as

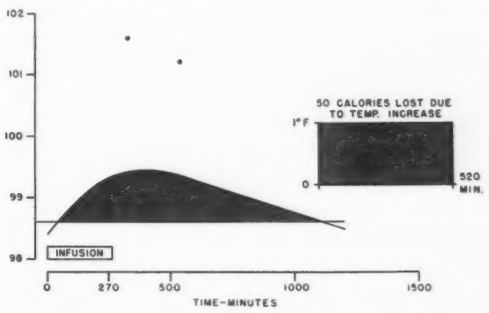

FIG. 2. The mean temperature elevation of 27 patients receiving 1,000 milliliter infusions (65 administrations) of fat emulsion was equivalent to a loss, as useless heat, of 4 per cent of the infused calories.

did Freeman and associates, that there was an increased proportion of injected fat removed by the end of infusion in cirrhotic patients compared with patients without cirrhosis. The converse of this, however, was striking in the patients with jaundice. The serum turbidity was measured during 7 of 9 infusions made in patients with jaundice and without reactions. The turbidity was higher and more prolonged in these cases than in patients without jaundice.

Waddell reported the incidence of chills and temperature elevation to be 2 to 6 times greater with postoperative infusions than with preoperative infusions. This observation is in agreement with our impression that fat emulsion was not as well tolerated

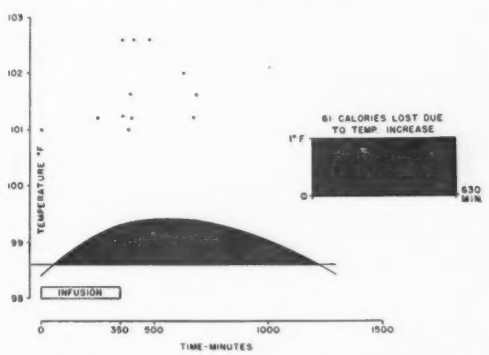

FIG. 3. The mean temperature elevation of 29 patients receiving 1,500 milliliter infusions (96 administrations) of fat emulsion was equivalent to a loss, as useless heat, of 4 per cent of the infused calories.

in the early postoperative periods as at other times. In view of our experience in cases of hepatic disease, altered hepatic function secondary to general anesthesia is a possible explanation for increased reaction in postoperative cases.

Patients with ulcerative colitis and regional enteritis tolerate fat emulsion poorly. The increased incidence of reactions observed in this group of cases may also have been the result of altered hepatic function secondary to these inflammatory diseases.

On two occasions we attempted to administer fat emulsion to a patient with severe adrenal insufficiency. Both infusions resulted in such prompt and serious reactions that we believe future administrations of fat emulsion to such patients should be undertaken with great caution.

Increased oxygen consumption associated with severe chills may increase myocardial ischemia. For this reason, the intravenous administration of fat emulsion is avoided in patients with severe cardiac disease.

Possibly the greatest deterrent to the intravenous use of fat emulsion has been the unexplained rise in temperature which occurs frequently. We have shown that only a small fraction of the infused calories was lost as useless heat, and we have observed no deleterious effects from the temperature rises. Although the cause and significance of temperature elevation remain unknown, the work of Lambert and Becker and their associates suggests that the speed with which fat leaves the circulating blood may have an important effect.

Our study shows that fat emulsion may be administered to a large percentage of patients without causing any adverse reaction. Reactions are not, therefore, a necessary or inevitable accompaniment of the injection of emulsified fat into the circulation. Since alimentary hyperlipemia is a normal, daily, physiologic occurrence, it is possible that a satisfactory means of duplicating this phenomenon by the intravenous injection of fat will be found. While emulsification of fat prior to infusion provides for some of the body's requirements for handling fat, the body's ability to meet other requirements which may be as essential, although less understood, will determine its tolerance for the abnormal egress of fat into the circulation. Further understanding of the physiologic mechanisms initiated by digestion and absorption of fat may contribute to the intravenous administration of fat without reactions. Certainly, the full list of clinical reactions is a formidable one, although many were of minor importance. At the same time, the unsatisfied daily caloric needs of surgical patients, who are dependent on parenteral nutrition, present a constant challenge. Much remains to be learned about the routine clinical use of intravenous fat emulsion. As understanding of the nature and incidence of the reactions to be expected increases, fear of these reactions can be expected to decrease. In this sense, our study supports those of other investigators who believe that fat emulsion can be administered intravenously with safety and benefit to selected patients for whom parenteral nutrition is of paramount clinical importance.

SUMMARY AND CONCLUSIONS

1. Fifteen different lots of an emulsion containing 10 per cent sesame oil, 0.65 per cent soybean phosphatides, and 4.5 per cent dextrose have been administered in 633 infusions to 209 patients. At the time of administration, the emulsion had been stored at room temperature for a maximal period of 5.2 months.

2. The character and incidence of reactions following the use of intravenous fat emulsion have been considered. Sixty-two per cent of all infusions were without side effects other than temperature changes, while 6 per cent were terminated because of reactions.

3. The effects of several variables on reaction rate have been studied. The greatest incidence of reactions occurred in patients with hepatic dysfunction.

4. Calculations made of the energy lost as a result of temperature elevations associated

with infusion of fat emulsion averaged 4 to 8 per cent of the calories administered. It is our opinion that such losses are not of any importance.

5. The marked variability of tolerance to fat emulsion manifested by different patients, and by the same patient on different occasions, suggests that reactions are due to unknown physiologic factors within the patient as well as to the structure and composition of the fat emulsion.

6. Intravenous fat emulsion should be withheld from patients with adrenal insufficiency or severe hepatic or cardiovascular disease.

7. Fat emulsion can be administered intravenously with safety and benefit to many patients who must depend entirely upon parenteral alimentation for nutrition.

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EDITORIALS

URINARY OBSTRUCTIONS IN CHILDREN

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OBSTRUCTION at the outlet of the urinary bladder is commonplace in senescent men, and laymen as well as physicians in general are aware of its frequent occurrence and are alert in recognizing it. Yet the occurrence of similar obstructive uropathy in children, though not uncommon, is less understood by the medical profession, with the result that physicians and parents alike often overlook certain abnormalities of micturitional behavior in infancy which, if recognized, would lead to early discovery. For the male infant normally urinates a forceful high trajectory stream, which is at once the object of curious pride to his mother as well as the envy of his father; and he empties his bladder with a continuous stream. Any male infant who does not emulate the boy made famous in the statue in Brussels and who urinates with an interrupted stream must be regarded with grave suspicion. Girls as well as boys may be afflicted with obstructive disorders but in the female the symptoms tend less to suggest obstruction than do the symptoms that occur in boys.

The commonest obstructive lesion in the male is stricture of the meatus which is easy of recognition and simple to treat by meatotomy. Boys also are occasionally afflicted with congenital valves in the prostatic urethra. These are thin membranous elevations that occur on the floor of the urethra and usually can be identified easily by endoscopy. Another cause of obstruction, occurring in both sexes, is contracture of the bladder neck. This is due probably more often to hypertrophy of the circular musculature—the so-called internal sphincter—than to fibrosis, and for this reason the obstructive lesion often is not readily identified endoscopically by intraluminal inspection. One female child with obstruction was found to have a ring of muscle, 2 centimeters in thickness, about the bladder outlet that resembled the lesion of pyloric stenosis.

Most often the presenting complaint is recurrent urinary infection that fails to respond permanently to any form of antibacterial medication, for obstruction enhances persisting infection, especially when there is residual urine. Troublesome enuresis in some instances will be found to result from obstruction and associated residual urine, and urinary incontinence by day is often the result of an advanced stage of this disease. When complete decompensation of the bladder musculature has occurred, there may be protuberance of the abdomen, and finally loss of appetite and apathy associated with uremia. The majority of cases, alas, are diagnosed when in the advanced stages. The diagnosis of urinary obstruction is usually made upon finding residual urine and observing gross trabeculation of the bladder—evidence of compensatory hypertrophy.

Advanced cases with serious impairment of renal function will require prolonged drainage for survival. Cases that are diagnosed before the occurrence of serious upper

urinary tract damage can be cured by removing the obstruction either endoscopically or by the retropubic approach. Most surgeons prefer the retropubic operation described by Bradford Young[1] which affords excellent exposure and can be performed with standard operating room instruments.

The present author read a short report on this subject a few years ago which was published in *The Michigan State Medical Society Journal*. Soon after its publication a physician in a nearby city phoned to state that he had read the article and had subsequently observed that his newborn grandson voided with hesitancy and interruption of the stream. Investigation revealed obstructing valves and residual urine amounting to 100 cubic centimeters. The obstruction was easily corrected by endoscopic procedure and one day later the infant was voiding freely and without interruption. He was saved from a life of urinary tract invalidism.

Early recognition is an all important factor in the successful management of these cases. Indeed, the well baby clinic should be the first line of attack in the early recognition of obstructive lesions. Doctors routinely instruct mothers of newborn babies regarding the care of their infants and inform them about certain observations that should be made from time to time, for example, bowel habits and sucking techniques. Equally important should be the observation of the act of micturition. Any evidence of impediment should prompt early investigation.

[1]YOUNG, BRADFORD W. The retropubic approach to vesical neck obstruction in children. Surg. Gyn. Obst., 1953, 96: 150-154.

WOUND HEALING

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THE REACTION OF TISSUE to injury is a phenomenon which the surgeon encounters so regularly in his daily practice that its basic implications are apt to escape him. Historically, the term "wound healing" recalls Paré's dressing of the open amputation stump with wine instead of boiling oil or Halsted's insistence on gentle handling of tissue and the advantages of fine sutures and ligatures. Since the classic contribution of Harvey and Howes, experimental studies of wound healing have been focused principally upon the rate in gain of tensile strength and the factors which alter it. Practically speaking, the thoughtful surgeon thinks of wound healing in terms of adequate blood supply, age of the patient, careful asepsis, avoidance of trauma, and the correction of nutritional deficiencies. All of this is vitally important, but is there not more for the surgeon to consider?

Broadly speaking, healing or repair is a fundamental feature of recovery from any injury or disease, but to the surgeon it should have particular significance. It is common to the clean, incised wound as well as the laceration or contusion; it occurs in the liver after shock and in the clot on the blood vessel wall in thrombophlebitis; it can be studied in the replacement of a vascular prosthesis by the host's tissue and in the bed of a duodenal ulcer, and it may play a crucial and as yet quite unappreciated role in the stromal reaction around an invading neoplasm. All of these states are "healing wounds" but evaluation of them in terms of histopathology and tensile strength alone is not likely to continue to be profitable. New methods are required.

During the last decade important advances have been made in our knowledge of the growth and metabolism of connective tissue. Electron microscopy, x-ray diffraction, histochemical staining methods, and direct chemical analysis have provided a wealth of new information. The use of isotope tracers, particularly C-14 labelled glycine and S^{35} labelled sulfate and methionine, have shown that mesenchymal tissues are metabolically very active. Connective tissue can no longer be regarded as a comparatively inert supporting tissue. It undergoes change in response to hormones, metabolic disturbances, and a great many disease states. Its reaction to local injury or irritation is quite variable. Moreover, it is now possible to distinguish among alterations in the ground substance, in the cellular reaction, and in the formation of collagen.

Much of this new knowledge is directly applicable to a study of wound healing, but to date surgeons have played a comparatively small role in these advances. In the next decade it is to be expected that the work of Asboe-Hansen, A. H. T. Robb-Smith, Karl Meyer, Bostrom, Duran-Reynals, Schmidt, and many others too numerous to mention will be as familiar to surgeons as it is to those whose primary concern is with collagen and the "collagen diseases."

Wound healing is a collagen disease and, as it receives more attention from surgeons, much new knowledge of universal practical applicability should be forthcoming.

THE SURGEON AT WORK

THE LATERAL FLAP TECHNIQUE IN SUPRACONDYLAR AMPUTATIONS

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ONE OF THE COMMON SURGICAL PROBLEMS in a general hospital is the treatment of gangrenous extremities in patients with arteriosclerosis or diabetes. These patients are predominantly elderly and emaciated. Their personal hygiene is either poor or nonexistent. If they are diabetic, they have little insight into their diabetes and its control. They usually have had the gangrenous process for a long period of time. Some have been content to watch an infected gangrene spread from the toes to above the knees. Many want to be left alone to die.

The treatment of arteriosclerotic or diabetic gangrene has been quite unsatisfactory. The diabetes is usually difficult to regulate because of the presence of infection. Secondary sepsis can be so fulminating that chemotherapy is ineffectual. Hospitalization is usually prolonged with a high morbidity rate, and a supracondylar amputation is usually required as a lifesaving procedure. In the past, the mortality rate for such amputations has varied from 25 to 50 per cent. More recently a mortality rate of 6 to 40 per cent has been reported. If an amputation has been performed, often the stumps heal poorly or require reamputation. In spite of the paucity of the current literature, amputations in these patients are still a problem which will increase in magnitude since more people are living to reach the later decades of life.

In an attempt to cope with this serious problem, a definite therapeutic plan has been used at Ancker Hospital since 1948. Certain prerequisites for surgery have been established, early amputations have been advised, and routine use of a lateral flap supracondylar amputation has been carried out. It is our purpose in this article to present some of the results which have ensued from this plan.

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GENERAL CONSIDERATIONS

The terms arteriosclerotic and diabetic gangrene have been used to describe the same pathologic process. The term arteriosclerotic gangrene is used henceforth to refer to both of these conditions.

Each patient seen in the emergency room or in consultation at Ancker Hospital who has arteriosclerotic gangrene is transferred to the peripheral vascular surgical service. Chemotherapy is started immediately in massive doses. Control of the diabetes and electrolyte balance are then given priority. The patient is placed at strict bedrest with the feet slightly elevated and protected by a cradle without heat. If it is possible, 24 hours or more are utilized to regulate the diabetes and improve the electrolyte imbalance, and to correct the anemia and check the cardiac status of the patient. If the signs and symptoms of the gangrene become limited during this initial period, sympathetic blocks or lumbar sympathectomy may be utilized. Supracondylar amputation is then postponed as long as improvement continues. If the patient fails to respond to 24 hours of such therapy or if the gangrene continues to spread, early amputation is advised.

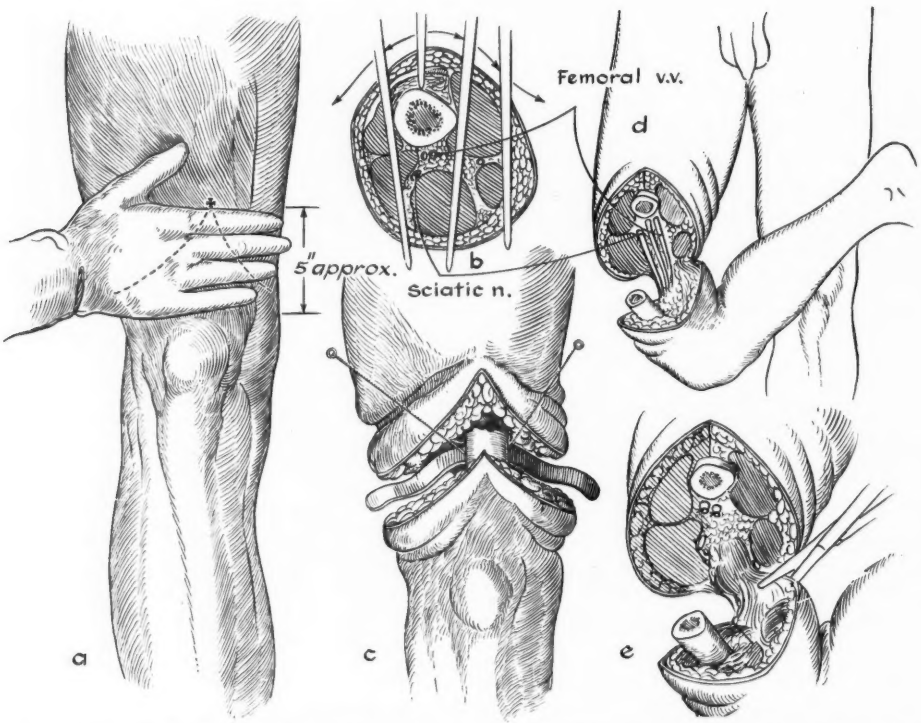

FIG. 1. a, Site of insertion of the long amputation knife. b, Cross sectional view of the method of forming the two lateral flaps. Note how the femoral vessels and sciatic nerve are protected by the femur. c, Placement of the malleable retractor and the use of the Gigli saw to sever the femur are shown. d, The leg is flexed and rotated to expose the great vessels and nerve. e, Amputation is completed by severing the posterior bundle of fat and skin.

CLINICAL CONSIDERATIONS

Since 1948, 103 patients with arteriosclerotic gangrene have undergone 114 supracondylar lateral flap amputations. All amputations have been performed by the resident staff under the supervision of the attending staff. The ages of the patients have varied from 35 to 94 years. The mean average age of 71.9 years is more than that reported in other series of similar patients. Sixty-two amputations were performed in men and 52 in women. There were 52 diabetics and 62 nondiabetics. Eleven patients (3 diabetic, 8 nondiabetic) had bilateral amputations.

The gangrenous process was a frank, wet, wild gangrene in 42 of the patients, 21 in diabetics and 21 in nondiabetics. Secondary sepsis was present in varying degrees of severity in all the remaining limbs. The right leg was affected 61 times and the left leg 53 times.

The average time interval between the onset of the symptoms of gangrene and admission to the hospital was 40.5 days in the diabetic patient and 54.4 days in the nondiabetic. The average time interval between onset of symptoms and time of surgery was 67.3 days in the diabetic and 55.2 days in the nondiabetic patients. Other studies have indicated that this delay by the patient may be partially responsible for one-third of the amputations in the arteriosclerotic patient.

A two stage procedure as carried out by Zierold, Pearse and Ziegler, and McLaughlin has not been used at Ancker Hospital. In our opinion, 2 anesthetics and 2 operative procedures, in all probability, would lead to an increase in the mortality rate. Prophylactic femoral vein ligation has not been employed at Ancker Hospital.

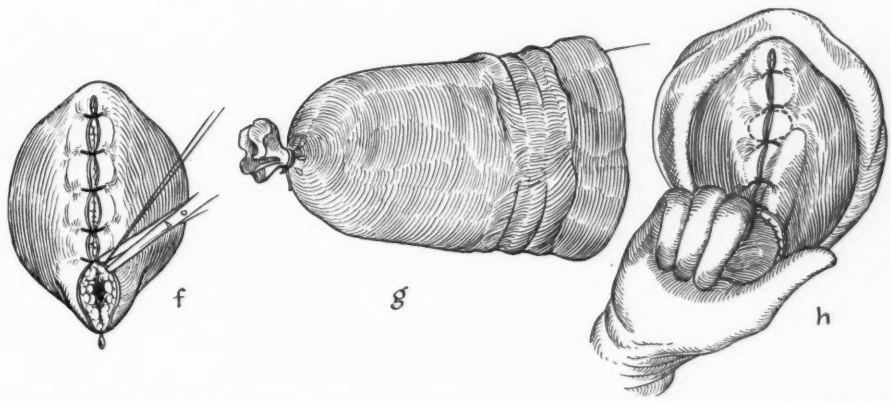

FIG. 1. f, The wound edge is sutured with only a few interrupted silk sutures in the skin. Note the posterior one-third of the wound is left open for drainage. g, The stockinet dressing is applied to the stump which is ready for application of traction. h, The sterile gloved finger is introduced into the posterior portion of the wound to drain any hematoma or collection of fluid.

LEVEL OF AMPUTATION

Before suggesting amputations below the knee in the arteriosclerotic patient certain facts deserve mention. Simple toe amputations carry a reported mortality rate of 2.2 to 16.6 per cent, and 32 to 50 per cent of these patients require reamputation at a higher level. Holden states that in 52.6 per cent of his amputations of the toe a thigh operation was necessary within 3 months. In 86.5 per cent of Eliason's amputations of the leg, thigh amputations were required. Amputation through the lower leg has a reported mortality of 4.8 to 42.9 per cent with a reamputation rate of 27.5 to 29 per cent. Amputation below the knee in the arteriosclerotic patient has been attempted at Ancker Hospital in a very few select cases. All patients have subsequently required a supracondylar amputation.

In a very select group of diabetic patients, McKittrick (3, 6) has been able to perform transmetatarsal amputations with excellent results. However, his criteria for selection of patients would not be met by any of the patients in our group.

The need of high amputations has been stressed by some authors and is based anatomically on the fact that the most common site of occlusion is at the bifurcation of the popliteal artery or distal femoral artery. The popliteal and genicular vessels about the knee are the only source of blood supply to the lower leg, the profunda femoris ending in the lower part of the thigh.

CHOICE OF ANESTHESIA

Anesthesia is usually a problem in these patients, and each patient must be treated on an individual basis. Spinal anesthesia has been the choice of many surgeons and was used in 100 of our cases. Pentothal augmented with nitrous oxide was used in 9 of our cases, and cyclopropane in 3 cases. Block anesthesia of the femoral and sciatic nerves with local infiltration of the area innervated by the obturator nerve was the choice in 2 cases. Ice refrigeration was used early in the series on a moribund patient who died soon after surgery.

LATERAL FLAP TECHNIQUE

The literature has dealt mainly with the indications for surgery or the level of the amputation, and little emphasis has been placed on the technique of the surgical procedure itself. Our criteria for a safe amputation include the following: a minimum of shock, ease of performance, dependent drainage, and minimal foreign body material for closure, and a well healed weight bearing stump. We also believe that the procedure should be one which can be used for a midthigh as well as a supracondylar amputation. In our hands, the lateral flap technique fulfills these criteria best.

It is recognized that the lateral flap technique for amputations is not as commonly used as some others, but we believe that when it is used, as outlined in the following, it causes minimal tissue damage and provides a stump that is easy

to convert into a totally closed stump without further surgery.

The patient is placed on the operating table in a supine position or even a semi-Fowler position if the cardiac status indicates. The entire affected limb and groin are prepared and draped in the usual manner with the lower leg being draped separately. A sharp pointed, long amputation knife is inserted through the anterior surface of the thigh at a level 4 to 6 inches above the patella until it touches the femur (Fig. 1a and b). The point of the knife is then worked around the lateral aspect of the femur and pushed posteriorly until the point emerges through the skin as near the midline as possible (Fig. 1b). The blade is then pushed distally and laterally so that a skin and muscle flap of 2 to 3 inches is formed. The knife blade is again placed in its original position on the anterior surface of the thigh. A medial flap of muscle and skin is formed in the same manner. The periosteum is scraped from the bone cortex to a point 2 inches above the apex of the incision. A malleable retractor is placed under the femur between the bone and the femoral artery and the vein and sciatic nerve. The femur is then transected with a Gigli saw 1½ inches above the apex of the incision (Fig. 1c). The leg is rotated 90 degrees and flexed to expose the great vessels and sciatic nerve (Fig. 1d). The vessels and nerve are then divided between clamps as high as possible and ligated with No. 000 chromic catgut. The remaining posterior bridge of tissue is divided to complete the amputation (Fig. 1e). Small bleeders are controlled with No. 000 and No. 0000 plain catgut ties.

At this point an appraisal is made of the appearance of the tissues. If the muscles appear dusky and ooze a little, poor wound healing can be anticipated and a second amputation is performed immediately at a level approximately 4 inches higher. This may be repeated until a level of good tissue viability is reached. A slight bloody ooze is desirable.

The skin is then approximated with sutures with no attempt at muscle or fascia approximation. The anterior two-thirds of the incision is closed loosely with the posterior portion left open for dependent drainage (Fig. 1f). No drains are used, and a dry dressing is applied. Skin traction is established by means of a stockinet glued to the skin with ace adherent (Fig. 1g). Postoperatively, 2 pounds of traction are used for 2 days. On the third postoperative day, the posterior portion of the wound is probed with a sterile gloved finger to the end of the femur in order to augment the drainage of any seromas or hematomas (Fig. 1h). This procedure is continued daily thereafter until the wound is completely healed. The stockinet may be left on indefinitely, and the dressing and probing may be performed through the end of the tubular dressing. If there are areas of nonviable tissue present in the wound these are radically débrided daily on the ward.

One of the advantages of the lateral flap technique is the ability to amputate at a level high enough to insure adequate circulation and good healing. This insurance is based on the surgeon's judgment of the tissue as he cuts across it. If the muscle tissue appears dusky and has little capillary ooze, the amputation is immediately repeated at a higher level. When a level is reached at which the muscle is beefy red and has a good capillary ooze, good wound healing can be anticipated. The difference between healing and not healing is only a hairline in the arteriosclerotic patient with arterial insufficiency.

Gentle tissue handling need only be mentioned for emphasis. The long amputating knife is not used by all surgeons. We believe that when the long amputation knife is used to form an entire muscle flap in one quick slash, a nontraumatized, smooth surfaced flap is formed. However, if a scalpel is used, the muscle surface of the flap is in many layers and has many crevices of traumatized tissue for potential foci of infection. Daily wound dressing and débridement of nonviable tissue reduce the incidence of infection.

RESULTS

Mortality rate. No single method for determining mortality rate among these patients exists in the literature. The number of deaths in our series according to the time interval from surgery to death was as follows: 6 in the 0 to 5 day interval group, 5 in 6 to 10 days, 5 in 11 to 15 days, 3 in 16 to 20 days, none in 21 to 25 days, 1 in 26 to 30 days, 2 in 31 to 45 days, none in 46 to 60 days, 1 in 61 to 90 days, 1 in 91 to 120 days, and 14 in the period over 120 days.

Inasmuch as the hospital stay of these patients is quite prolonged for reasons sometimes unrelated to their amputations, we have decided that a death occurring 30 or more days postoperatively unrelated to the procedure per se should not

be classified as an operative death. In the Ancker Hospital series of 114 amputations in 103 patients, there were 20 surgical deaths, a patient mortality of 19.41 per cent and an operative mortality of 17.54 per cent.

Postoperative mortality. The cause of postoperative death was noted to be: bronchopneumonia in 6 cases, pulmonary emboli, embolic cerebral vascular accident, and mesenteric thrombosis in 4, cardiac decompensation in 4, unknown in 3, uremia in 2, and cardiac arrest in 1 case. Bronchopneumonia was the leading cause of death. Embolic phenomena and cardiac decompensation were the second most common causes of death.

Hospital morbidity. There are many times at Ancker Hospital when the postoperative stay in the hospital is unduly prolonged by the fact that this is a community center for domiciliary care of patients awaiting disposition in nursing homes and county farms. The length of the postoperative hospitalization averaged 38.2 days for diabetic patients and 42.3 days for the nondiabetic patients. Many factors tend to increase the length of hospitalization for these elderly patients who have lost a limb from arteriosclerosis. Their recuperative powers are inherently poor because of inadequate nutrition, diabetes, anemia, decreased blood volume, and poor renal and cardiac reserves. In spite of medical armamentarium for diagnosis and therapy to overcome these factors, the patient's desire to give up must be overcome. These patients usually believe the end is near when they lose a leg. Many realize that they will be entirely dependent upon others and do not care for this prospect. One has to contend with the economic and emotional problems of the homes from which these patients come, or with the unenlightened response of relatives even though the patients are from institutions in the community. The fact is obvious that often these patients are unwanted and their demise often affords some degree of relief to an already overburdened family.

Healing of stumps. Primary wound healing occurred in 85, or 75.4 per cent of the cases. Poor wound healing as evidenced by partial wound dehiscence or by stump infection occurred in 3 cases (2.4 per cent). No healing, requiring reamputation, occurred in 11 patients (9.2 per cent), 1 of whom at death was listed as a surgical fatality. In 15 cases, the recorded evidence was insufficient to classify the type of wound healing accurately, or the patient died too soon after surgery was carried out to permit healing of the stump to begin.

No patient has been denied a prosthesis for lack of a good stump. No difficulty from the fitting of the prosthesis has been encountered to date. The limiting factor in the fitting and use of a prosthesis has been the mental attitude of the patient and his physiologic age.

DISCUSSION

We do not accept the operative mortality of 17.5 per cent in this series as being optimum. Certain factors involved are fixed and others not. The factors which cannot be changed include the age and physiologic condition of the patient. The greatest factor that can be improved upon is the delay between the onset of the symptoms and the time of amputation. Such improvement requires the education of the public in seeking early care. However, after the patient has finally been admitted to the hospital, the staff, attempting to be conservative in the hope of salvaging the extremity, has indeed often delayed too long an amputation which was obviously necessary when the patient was first seen.

In our hands the technique described has proved to be very effective. It is simple, easily standardized, and in this series has been done entirely by the resident staff. It is equally adaptable as an elective or as an emergency procedure. In the former, primary wound healing, minimum morbidity, and a good useable stump are usually assured. In the latter, it has proved an excellent emergency procedure in that it can be done as rapidly as a guillotine procedure and offers all the advantages thereof. In such a situation, the lower one-third or one-half of the wound can be left unclosed and approximated at a later date without a secondary revision.

SUMMARY AND CONCLUSION

1. Arteriosclerotic gangrene is a fulminating type of gangrene that requires lifesaving amputation. The patients are elderly and extremely poor risks.

2. The experience of the Ancker Hospital staff with the lateral flap supracondylar amputation is presented.

3. Use of the lateral flap in our hands has had many advantages, has provided an acceptable mortality as well as good healing and a satisfactory stump.

4. Delay on the patient's part in seeking medical aid has influenced final recovery.

5. After hospitalization, added delay by the physician in charge in his hope to save a limb has further compromised the outcome. This tendency, more common in the earlier part of the series reported, is currently being corrected.

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THE SURGEON'S LIBRARY

Reviews of New Books

THERE ARE FEW REGIONS of the body in which there arise more discussions and differences of opinion as to roentgen interpretations than the cervicodorsal region. Actually, however, the incidence of anomalies and anatomic variations is more rarely encountered in that region than in the lumbosacral region.

The author, one of the world's outstanding authorities on skeletal roentgenology, has set forth in his work entitled *Die occipito-cervical-Gegend*[1] the roentgen anatomic relations of the cervical and upper dorsal vertebrae and the various pathologic states which may be encountered. In the course of this investigations the author has become more and more impressed with the necessity of employing an individual technique adapted to the case in hand rather than a routine standard technique of examination. In neurology the recognition of anomalies has become increasingly important.

A comprehensive bibliography is included, which fairly well includes the American literature. The illustrations are exceptionally well reproduced. This interesting monograph merits abundant praise, though it needs the supplement of the information very recently developed by Jacobson of the Los Angeles (California) General Hospital. —*James T. Case.*

THE TEXTBOOK *Embryologie*[2] by the Professor of Anatomy at the University of Frankfurt departs considerably from the usual product emanating from anatomic laboratories of medical schools. Its final focus is man, but the treatment of human development gives ground to extended considerations of development in lower mammals, in other vertebrates and, to a degree, in invertebrates. It is the author's belief that the findings in experimental morphogenesis and developmental physiology, gained from lower vertebrates and from invertebrates, provide an important basis for the understanding of the proper significance of many biologic problems, including those of pathology and clinical medicine. Accordingly, various aspects of experimental biology and causal development are reviewed. The result is a treatise of human development with a considerable general biologic, experimental, and comparative bias. This has distinct advantages from the standpoint of broad outlook, whereas the concomitant limitations of space prevent such extended considerations of human development as the size of the book might lead one to expect. The treatment is modern; the illustrations are satisfactory but not profuse in comparison to the attempted coverage; there is a valuable bibliography and an adequate index. For those who seek information on development in forms other than man, and for those who are curious as to what the experimentalists have done in unravelling the dynamic relations in causal development, this book should offer particular appeal.

—*Leslie B. Arey.*

THE VOLUME of 143 pages entitled *Roentgenschichtverfahren*[3] gives a succinct account of the development of body section roentgenography, but with only casual reference to the early work of the American contributors to this subject. The contribution of Sherwood Moore and his associates has apparently been omitted entirely from the historical chart. The theoretic and historical and technical considerations are described satisfactorily in great detail, with an abundance of illustrative drawings. There are 92 excellent illustrations which convince one of the value of tomography in supplying detail not otherwise to be achieved in a certain number of internal pathologic states, particularly abscess and other lung lesions, bronchogenic detail, particulars of certain anatomic conditions, such as the atlantoaxoid articulation, the sternum, and the larynx, for example. No space has been devoted to the most recent development of tomography in which transverse axial sections can be depicted. This transversoaxial projection is especially valuable in determining the operability of thoracic cancer. The complicated and expensive equipment necessary for this type of work will hinder its general use for some time to come. Improvised methods of tomography expose the radiologist or his technician to so much radiation that their use cannot become routine. This method can be made perfectly safe for patient and operator if sufficient funds are available. —*James T. Case.*

[1]DIE OCCIPITO-CERVICAL-GEGEND; EINE DIAGNOSTISCH-PATHOGENETISCHE STUDIE. By Priv.-Doz. Dr. J. E. W. Brocher. 145 pages, 91 illustrations. DM 48. Stuttgart: Georg Thieme Verlag, 1955.

[2]EMBRYOLOGIE; EIN LEHRBUCH AUF ALLGEMEIN BIOLOGISCHER GRUNDLAGE. By Dietrich Starck. 688 pages, 502 illustrations. DM 78. $18.55. Stuttgart: Georg Thieme Verlag, 1955.

[3]ROENTGENSCHICHTVERFAHREN; GRUNDLAGEN DER TECHNISCHEN ENTWICKLUNG UND DER KLINISCHEN ANWENDUNG FUER DIE PRAXIS. By Prof. Dr. R. Griesbach and Dr. F. Kemper. 143 pages, 187 illustrations. DM 39. Stuttgart: Georg Thieme Verlag, 1955.

THE SECOND VOLUME of *Clinical Roentgenology*[4] calls for commendation, as did the first. The writers are men of wide experience, and they have had access to a vast amount of material from which they have selected well. With few exceptions, even the untutored eye can gain impression of the entity which they are trying to present. In this volume they undertake to review the contributions of x-ray diagnosis of the skull, facial bones, and spine. They have covered this material with great completeness.

To assist in an understanding of the lesions described, they review the development of the bones of the skull. They present helpful information about the technique of making skull films. The authors then discuss at reasonable length and in considerable detail, the normal roentgen anatomy of the skull. This introductory chapter is then followed by an extensive bibliography.

Shortly after receiving this book for review, this reviewer had in hand a case of hyperostosis frontalis interna. He had not previously encountered such a case in his practice and found the description and the photographs very helpful in understanding this condition. Further reading concerning this entity has lead this reviewer to commend the clinical description particularly. There is an excellent short review of angiography with helpful anatomic diagrams accompanying it. The section on brain tumors seems particularly complete and well done. To one not specializing in x-ray interpretation the photographs which illustrate maxillofacial fractures are extremely helpful and very instructive.

For the general surgeon, the section on the neck and spine is very useful. A quick review of this section of the book will help anyone confronted with accident cases to know better what he is dealing with and when he will need to disturb the x-ray man in off hours to come in for interpretation. There is a particularly useful section concerning the problem of intervertebral discs; and at the beginning of the whole section of the spine there is a helpful review of the anatomy which enables one to understand the pathology of the region better, as well as to interpret the x-ray films with greater understanding.

In reviewing the first volume it was believed by this reviewer that there was considerable unused space on some of the pages. It seems this time a great economy has been exercised and that this criticism does not apply to this volume. The publishers have again done an excellent job in producing clear reproductions of the radiographs selected. They have again used high grade paper and clear inking in producing the volume. This book is recommended again as a valuable reference for both specialists and general medical men.

—*Martin B. Tinker, Jr.*

THE AUTHOR'S laboratory observations, clinical experiences, and several new ideas on the basic mechanism are combined in a very nice way in the 150 page monograph on *The Mechanisms of Healing in Human Wounds*.[5] Too often we are prone to put "stuff to stuff" in our surgical closures and thereby frequently jeopardize the function of the part because of wound inflammation, secretions, and granulations.

Wounds, whether they be burns, ulcers, or surgical incisions, heal by two distinct processes; fibrous healing of the deeper layers including the dermis and epithelial healing. Epithelization takes place by the ameboid movement into the wound of the cells from all layers of the surrounding epithelium. Mitosis takes place secondarily and occurs late in the process of healing. The surface which can be covered by these cells is dependent upon the number of living epithelial cells and the surface over which they are to extend. The deeper fibrous healing results from a deposit of collagen, produced by cells which were not previously part of the functioning tissue involved in the injury. The author believes that the lymphocyte is a cell of varied potentialities, and substances resulting from its disintegration at the wound site are the precursors of collagen.

The latter half of the book deals with topics such as infection, time factors, age of the patient, physical factors, and their effect on wound healing. Complications such as wound dehiscence, postoperative hernia, and adhesions are presented as to cause and effect. Healing of burns, ulcers, and donor sites are handled briefly, but one no longer asks: "Why should this be covered with skin?" or "What is the dressing of choice?"

The American Lecture Series is enhanced by this volume—a thought provoking book for both teacher and student alike. —*W. B. Stromberg, Jr.*

A COMPLETE TREATISE on cancer cells is ably presented in the book entitled *Cancer Cells*.[6] It deals with many of the problematic aspects in oncology, i.e., the properties of malignant cells, particularly on physicochemical and histochemical grounds, carcinogenesis, and the author's personal evaluation of the data thus far presented by various workers in support of their hypotheses on the subject. Factors which may alter cancer production and formation such as diet and geographic environment, and data on diagnosis, prevention, and treatment are incorporated. The technical terms are defined and discussed clearly. A brief summary is included at the end of each chapter lending compactness and integration to the volume. All authors and their publications cited in the book are listed in a separate bibliography for convenience of the reader. The aim of the author is to introduce the reader to the more important facts about cancer, culled from past and present literature.

Theories and concepts, which are carefully analyzed and arranged into cogent chapters to supply clues for further avenues of investigations, are more than adequately tabulated in this book.

The print is clear, on a good grade of glossed paper, and the tome is expertly bound. Particular attention is directed toward the appendix and its purpose. Tables

[4]CLINICAL ROENTGENOLOGY. Vol. II. THE HEAD, NECK AND SPINAL COLUMN. By Alfred A. de Lorimier, M.D., Henry G. Moehring, M.D., and John R. Hannan, M.D. 464 pages, illustrated. $18.50. Springfield, Ill.: Charles C Thomas, 1954.

[5]THE MECHANISMS OF HEALING IN HUMAN WOUNDS; A CORRELATION OF THE CLINICAL AND TISSUE FACTORS INVOLVED IN THE HEALING OF HUMAN SURGICAL WOUNDS, BURNS, ULCERS, AND DONOR SITES. By Shattuck W. Hartwell, B.S., M.S., M.D., Ph.D. in Surgery, F.A.C.S., F.I.C.S. 166 pages, 44 illustrations. $4.75. Springfield, Ill.: Charles C Thomas, 1955.

[6]CANCER CELLS. By E. V. Cowdry. 677 pages, 137 illustrations. $16.00. Philadelphia and London: W. B. Saunders Co., 1955.

are expertly assembled and used to supplement written data.

The volume should be recommended for ready and universal use. —*Mark C. Wheelock.*

THE METHODS AND MATERIALS used by the author in his office practice are presented in *Office Procedures*,[7] written by Paul Williamson. It contains 412 pages and has an abundance of illustrations which greatly assist the descriptions. All fields of medicine and surgery are covered and in each section good methods of examination are first presented followed by a description of treatment.

Good surgical practice, however, requires that surgery be done under the best possible conditions, and it is doubtful if many of the procedures described by the author should be undertaken outside of a well equipped operating room. It is conceivable that in areas remote from such facilities there may be times when some of these procedures could justifiably be done in the office. It is under these conditions that this book is probably of most value. —*Russell T. Bothe.*

IN THE BEGINNING PAGES of the monograph entitled *La pression interfragmentaire dans l'osteosynthèse*,[8] the author, J.-P. Razemon, discusses the histologic viewpoints on fracture healing and considers especially healing "per primam intentionem," as he calls it, which means "without the formation of an apparent bony callus."

Of the different factors which are involved in such a healing process, it is certainly the axial pressure on the fracture ends which is the most important one but other conditions have to be met with. Not in every fracture nor at any stage of the repair process can this healing per primam be obtained. To obtain a true healing without visible fracture line or visible callus necessitates an open reduction and fixation with pressure between the bone ends within the first 2 days after the accident. The techniques and the devices by means of which an axial pressure can be obtained in experimental surgery and in man, and the results of these techniques in the author's own cases, are described in detail.

The best results seem to be obtained in fractures of the forearm, oblique fractures of the tibia, and in nonunion without gross displacement, where the pressure exerted on the fracture ends by the coaptation bone plates acts as an irritating factor causing union. —*J. Mulier.*

AN INTERNATIONAL SYMPOSIUM on Cardiovascular Surgery[9] was held in Detroit, Michigan on March 17, 18, and 19, 1955, sponsored by the Henry Ford Hospital. The participants and discussants came from many cardiovascular centers throughout the world. It was the most unique concentrated gathering of its kind, invited to consider and discuss the various phases of cardiovascular surgery. Studies concerning diagnostic methods, normal and abnormal physiology, pathology, and surgical techniques were well presented and discussed.

Sixty participants' and 17 discussants' papers presented at this meeting were edited by Dr. Conrad Lam, the Chairman of the Henry Ford Hospital Committee, and were published by W. B. Saunders Company. The result is the most up-to-date publication concerned with surgery of the heart, of the great vessels, and of the peripheral vessels. The editor and the hospital are to be congratulated on sponsoring this symposium and on collecting and editing the many valuable papers which are included in this one well illustrated book of 543 pages. —*Egbert H. Fell.*

A DETAILED DESCRIPTION (188 pages) of the author's anatomic studies of the parametrium is presented in the volume entitled *Das Parametrium*[10] by Wilhelm Langreder. In this work, the author follows the thinking of his illustrious predecessors who include Hegar, Sellheim, and Wolf in his careful studies of morphology and function. He concludes that the endopelvic fascia is continuous with the cervical fascia and that these two structures are in reality one structure. Furthermore, he shows that they function as a unit during coitus, pregnancy, delivery, and puerperium. There is also included a complete and meticulous bibliography of 21 pages on the subject. This thesis is very well illustrated and the book makes excellent detailed reading for those who are interested in this subject.

—*Ralph A. Reis.*

THE SECOND EDITION of a book on the back by Dr. Lewin is entitled *The Back and Its Disk Syndromes*.[11] The first edition was known as *Backache and Sciatic Neuritis*. The text comprises approximately 900 pages and covers practically all of the disorders of the back. A maximum amount of space is devoted to the problem of the low back, including the herniated intervertebral disc.

The author has used his own valuable experience in combination with the material written by the world authorities for the past 40 years, to present a very comprehensive survey of back problems. The nonoperative and office management of these problems is emphasized throughout the book. The book is easy to read, is well illustrated, and well summarized.

—*Webster B. Gelman.*

[7] OFFICE PROCEDURES. By Paul Williamson, M.D. 412 pages, illustrated. $12.50. Philadelphia and London: W. B. Saunders Co., 1955.

[8] LA PRESSION INTERFRAGMENTAIRE DANS L'OSTEOSYNTHÈSE. By Docteur Jean-Pierre Razemon. 123 pages, illustrated. Lille: Imprimerie Morel et Corduant, 1955.

[9] HENRY FORD HOSPITAL INTERNATIONAL SYMPOSIUM ON CARDIOVASCULAR SURGERY; STUDIES IN PHYSIOLOGY, DIAGNOSIS, AND TECHNIQUES. Proceedings of the Symposium held at Henry Ford Hospital, Detroit, Michigan, March 1955. Edited by Conrad R. Lam, M.D. 543 pages, illustrated. $12.75. Philadelphia and London: W. B. Saunders Co., 1955.

[10] ZWANGLOSE ABHANDLUNGEN AUF DEM GEBIETE DER FRAUENHEILKUNDE. Edited by Prof. Dr. Robert Schröder. Vol. 18. DAS PARAMETRIUM; FUNKTIONELLE ANATOMIE DER LIGAMENTZUEGE SOWIE IHRE BEZIEHUNG ZUR ZERVIX UND BECKENWAND BESONDERS WAEHREND DER SCHWANGERSCHAFT UND GEBURT. By Wilhelm Langreder. 188 pages, 122 illustrations. DM 33.50. Leipzig: Veb Georg Thieme, 1955.

[11] THE BACK AND ITS DISK SYNDROMES; INCLUDING INJURIES, DISEASES, DEFORMITIES AND DISABILITIES WITH NOTES ON THE PELVIS AND COCCYX. By Philip Lewin, M.D., F.A.C.S., F.I.C.S. 2nd ed., thoroughly revised. 942 pages, 371 illustrations and 4 color plates. $18.50. Philadelphia: Lea & Febiger, 1955.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

AN ATLAS OF OTOLARYNGIC PATHOLOGY. By Colonel J. E. Ash, R.A. (Ret'd), M.D., and Muriel Raum, M.D. 572 pages, 2024 figures on 420 plates, 2 color. $20.00. Published under the Joint Sponsorship of The American Academy of Ophthalmology and Otolaryngology, The American Registry of Pathology, and The Armed Forces Institute of Pathology. Washington, D. C.: American Registry of Pathology, 1956.

DISEASES OF THE CHEST. By H. Corwin Hinshaw, M.D., Ph.D., and L. Henry Garland, M.B., B.Ch. 727 pages, 634 illustrations on 288 figures. $15.00. Philadelphia and London: W. B. Saunders Co., 1956.

A MODERN PILGRIM'S PROGRESS FOR DIABETICS. By Garfield G. Duncan, M.D. 222 pages, illustrated. $2.50. Philadelphia and London: W. B. Saunders Co., 1956.

PRINCIPLES OF RENAL PHYSIOLOGY. By Homer W. Smith, A.B., Sc.D., M.S.(Hon.). 237 pages, 24 illustrations. $5.00. New York: Oxford University Press, 1956.

THE DIAGNOSIS AND MANAGEMENT OF UROLOGICAL CASES; A HANDBOOK FOR STUDENTS, RESIDENTS AND GENERAL PRACTIONERS. By Bruce W. T. Pender, M.B., B.S., F.R.C.S., and James O. Robinson, M.A. (Cantab.), M.Chir., F.R.C.S. 170 pages, 48 illustrations. $5.00. Baltimore: The Williams & Wilkins Co.; London: Baillière, Tindall & Cox, 1955.

NEURAL CONTROL OF THE PITUITARY GLAND. By G. W. Harris, F.R.S., ScD., M.D. 298 pages, 54 illustrations. $6.75. Baltimore: The Williams & Wilkins Co.; London: Edward Arnold (Publishers) Ltd., 1955.

SURGICAL DIAGNOSIS. By Philip Thorek, M.D., F.A.C.S., F.I.C.S. With drawings by Carl T. Linden. 320 pages, 291 illustrations. $12.00. Philadelphia and Montreal: J. B. Lippincott Co., 1956.

FRACTURES OF THE FACIAL SKELETON. By N. L. Rowe, F.D.S.R.C.S.(Eng.), and H. C. Killey, F.D.S.R.C.S. (Eng.). 923 pages, 1231 illustrations, 14 in color. $22.00. Baltimore: The Williams & Wilkins Co., 1955.

DIAGNOSIS AND TREATMENT OF VASCULAR DISORDERS (ANGIOLOGY). Edited by Saul S. Samuels, A.M., M.D., F.A.C.A., F.A.C.C. 621 pages, illustrated. $16.00. Baltimore: The Williams & Wilkins Co., 1956.

ROENTGENOLOGISCHE DIFFERENTIALDIAGNOSE DER KNOCHENERKRANKUNGEN. By Dr. Hans Hellner and Dr. Hanno Poppe. 903 pages, 518 illustrations. DM 270. —$64.35. Stuttgart: Georg Thieme Verlag, 1956.

ERGEBNISSE DER GESAMTEN TUBERKULOSEFORSCHUNG. Edited by St. Engel, L. Heilmeyer, J. Hein, and E. Uehlinger. Vol. XIII. 659 pages, 160 illustrations. DM 96.—$22.85. Stuttgart: Georg Thieme Verlag, 1956.

CLINICAL MANAGEMENT OF RENAL FAILURE. By Maurice B. Strauss, M.D., and Lawrence G. Raisz, M.D. 114 pages, 2 illustrations. $2.75. Springfield, Ill.: Charles C Thomas, 1956.

ANESTHESIA; THIEF OF PAIN. By Sylvan M. Shane. 87 pages, 3 illustrations. $2.50. New York: The Vantage Press, 1956.

OBSTETRIC PRACTICE. By Harold Speert, M.D., and Alan F. Guttmacher, M.D. 478 pages. $7.00. New York: Landsberger Medical Books Inc.; distributed solely by The Blakiston Division of the McGraw-Hill Book Co., 1956.

OPERATIVE TECHNIC IN SPECIALTY SURGERY. Edited by Warren H. Cole, M.D., F.A.C.S. With 67 contributing authors. 2nd ed. Introduction by Allen O. Whipple. 976 pages, illustrated. $20.00. New York: Appleton-Century-Crofts, Inc., 1956.

CLINICAL LABORATORY DIAGNOSIS. By Samuel A. Levinson, M.S., M.D., Ph.D., and Robert P. MacFate, Ch.E., M.S., Ph.D. 5th rev. ed. 1246 pages, 244 illustrations and 13 plates, 11 in color. Philadelphia: Lea & Febiger, 1956.

SUBPHRENIC ABSCESS. By H. R. S. Harley. 216 pages, 35 illustrations. $7.00. Springfield, Ill.: Charles C Thomas, 1956.

THE CERVICAL SYNDROME. By Ruth Jackson, B.A., M.D., F.A.C.S. 130 pages, 50 illustrations. $4.75. Springfield, Ill.: Charles C Thomas, 1956.

"CONTROLLED HYPOTENSION" IN ANESTHESIA AND SURGERY. By David M. Little, Jr., M.D. 159 pages, 14 illustrations. $4.50. Springfield, Ill.: Charles C Thomas, 1956.

MODERN OPERATIVE SURGERY. Edited by the late G. Grey Turner, LL.D., D.Ch., M.S., F.R.C.S., and Lambert Charles Rogers, V.R.D., M.Sc., M.D., F.R.C.S. 4th ed., 2 vols., Vol. I. 1229 pages, 476 illustrations. $15.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1956.

HANDBUCH DER GESAMTEN UNFALLHEILKUNDE. Edited by Prof. Dr. H. Burkle de la Camp and Prof. Dr. P. Rostock. 2nd rev. ed., Vol. III of a 3 volume set. 701 pages, 134 illustrations. DM 105. Stuttgart: Ferdinand Verlag, 1956.

THE CELLULAR BASIS OF WOUND REPAIR. By Martin Allgower, M.D. 125 pages, 45 illustrations. Springfield, Ill.: Charles C Thomas, 1956.

LEHRBUCH DER GYNAEKOLOGIE. By Prof. Dr. Med. Heinrich Martius. With the collaboration of Kathe Droysen. 4th rev. ed. 414 pages, 446 illustrations. DM 49.80. Stuttgart: Georg Thieme Verlag, 1956.

LE CANCER DU PLANCHER DE LA BOUCHE. By Marcel Dargent and Jean Papillon. With the assistance of J.-F. Montbarbon. 170 pages, 48 illustrations. 1.800 fr. Paris: Masson & Co., 1955.

SKIN SURGERY. By Ervin Epstein, M.D. 228 pages, 242 illustrations on 101 figures. $7.50. Philadelphia: Lea & Febiger, 1956.

THE PREGNANCY TOXEMIAS OR THE ENCYMONIC ATELOSITESES. By G. W. Theobald, M.A., M.D.(Camb.), F.R.C.S.(Edin.). 488 pages, 56 illustrations. $15.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1956.

THERAPY OF FUNGUS DISEASE; AN INTERNATIONAL SYMPOSIUM. Edited by Thomas H. Sternberg, M.D., and Victor D. Newcomer, M.D. Presented by the Division of Dermatology, School of Medicine, University of California at Los Angeles. 337 pages, illustrated. $7.50. Boston and Toronto: Little, Brown & Co., 1955.

DIE FRUEHDIAGNOSE DES UTERUSCARCINOMS; HISTOLOGIE KOLPOSKOPIE, KOLPOPHOTOGRAHIE, CYTOLOGIE, BIOCHEMISCHE METHODEN. By Prof. Dr. Med. Hans Limburg. 334 pages, 122 illustrations. 3rd enl. rev. ed. DM 36.— $8.60. Stuttgart: Georg Thieme, 1956.

ÉTUDE RADIO-ANATOMIQUE DE L'OS TEMPORAL. By M. Juster and H. Fischgold. 106 pages, 51 illustrations. 2.800 fr. Paris: Masson & Co., 1955.

CHIRURGIE DES GLANDES SALIVAIRES. By Henri Redon. 282 pages, 77 illustrations. 2.900 fr. Paris: Masson & Co., 1955.

ATLAS DER KOLPOMIKROSKOPIE. By Prof. Dr. Tassilo Antoine and Doz. Dr. Viktor Grünberger. 224 pages, 176 illustrations. Stuttgart: Georg Thieme Verlag, 1956.

FILMS MEDICAUX ET CHIRURGICAUX FRANÇAIS. Assembled by Dr. Philippe Détrie. 302 pages. 1.600 fr. Paris: Masson & Co., 1956.

AMERICAN COLLEGE OF SURGEONS

WARREN H. COLE, Chicago, *President*

DANIEL C. ELKIN, Lancaster, Kentucky, *President-Elect*

PRELIMINARY PLANS FOR THE 42nd CLINICAL CONGRESS THE CIVIC AUDITORIUM, SAN FRANCISCO, CALIFORNIA OCTOBER 8 TO OCTOBER 12, 1956

THE 42ND CLINICAL CONGRESS of the American College of Surgeons will be held in San Francisco, October 8 through 12. The Civic Auditorium will be headquarters for registration, ciné clinics, color television, medical motion pictures, principal scientific sessions, and some postgraduate courses. Other sessions will be held at the Fairmont, Mark Hopkins, Sheraton-Palace, and Sir Francis Drake Hotels.

Plans for the Congress, as they develop, will be published in this Journal each month. The final program will appear in the September number. General plans for the Congress will follow those of previous years.

1. Eight postgraduate courses will be given, meeting Monday through Thursday, with the exception of Obstetrics and Gynecology which will meet through Friday.

2. The Martin Memorial Lecture will be given Monday evening, and the Presidential Address on Friday evening. Again this year the Oration on Trauma will be heard Thursday afternoon.

3. The ciné clinic and medical motion picture program, approved by the College's Committee on Motion Pictures, with H. P. Jenkins of Chicago as Chairman, will be held mornings and afternoons all week.

4. Drs. H. Glenn Bell, San Francisco, and J. Garrott Allen, Chicago, are in charge of the television program, which will emanate from the H. C. Moffitt Hospital. Introduced last year, the two-way programs with audience participation were highly successful and will be continued.

San Francisco Committee on Arrangements

Dr. Frank Gerbode is Chairman of the local Advisory Committee on Arrangements for this year's Congress, Dr. Horace J. McCorkle is Vice Chairman, and Dr. Orville F. Grimes is Secretary. Serving under Dr. Gerbode on this committee are the following Fellows of the College:

LEROY C. ABBOTT
PHILIP N. BAXTER
H. GLENN BELL
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Official Meetings

Only two general evening sessions will be held, plus the popular Motion Picture Symposium. On the opening evening, Dr. Gerbode will welcome visitors to the Congress, Dr. I. S. Ravdin, Chairman of the Board of Regents, will introduce guests, and Dr. Vannevar Bush, Washington, will give the Martin Memorial Lecture. The Convocation will be held the final evening, Friday, October 12. At this event Initiates will be presented for fellowship, honorary fellowships conferred, and officers inaugurated. Dr. Daniel C. Elkin, Lancaster, Kentucky, incoming President of the College, will give the Presidential Address.

The historic Oration on Trauma, first given in 1929, when it was known as the Fracture Oration, will be given this year by Michael L. Mason, Chicago, on Thursday afternoon at 3:15. His topic is: "Treatment of Open Wounds."

Tuesday, Wednesday, and Thursday evenings will be held open for the Motion Picture Symposium and other special group activities.

General Sessions

The general sessions will begin this year on Monday, October 8, at 10 a.m. Subjects of the general sessions follow:

MONDAY, 10 a.m.—Panel discussion on Surgery of the Adrenal Glands; 1:30–3 p.m.—Panel discusion on Prophylaxis in Dissemination and Implantation of Cancer; 3:30–5 p.m.—Panel discussion on Hyperthyroidism.

TUESDAY, 1:30–3 p.m.—Panel discussion on Pelvic Pain in Women; 2–5 p.m.—Symposium on Trauma; 3:30–5 p.m.—Panel discussion on Surgical Management of Duodenal Ulcer.

WEDNESDAY, 1:30–3 p.m.—Panel discussion on Hiatal Hernia and Esophagitis; 2–5 p.m.—Symposium on Cancer; 3:30–5 p.m.—Panel discussion on What Antibiotics Should We Use, and When?

THURSDAY, 1:30–3 p.m.—Panel discussion on Burns; 1:30–3 p.m.—Symposium on Graduate Training; 3:15 p.m.—Oration on Trauma: The Treatment of Open Wounds.

FRIDAY, 9 a.m.–12 noon.—What's New in Surgery?

Specialty Sessions

Panel discussion subjects for the specialty sessions, being arranged by their Advisory Councils, are briefly outlined here:

OBSTETRICS AND GYNECOLOGY

MONDAY, 1:30–3 p.m.—Prematurity and Postmaturity; 3:30–5 p.m.—Metabolic Impact of Surgery, Radiation and Labor.

TUESDAY, 1:30–3 p.m.—Pelvic Pain in Women; 3:30–5 p.m.—Contrasted Methods in Treatment of Abruptio.

WEDNESDAY, 2–5 p.m.—Surgical Forum session.

THURSDAY, 1:30–3 p.m.—Perineal Trauma.

FRIDAY, 1:30–3 p.m.—Indications and Techniques in Induction of Labor; 3:15–4:45 p.m.—Surgical Standards in Treatment of Carcinoma of the Cervix.

UROLOGY

MONDAY, 3:30–5 p.m.—Hypospadias

TUESDAY, 1:30–3 p.m.—Evaluation of Isotopes in the Treatment of Carcinoma of the Prostate and Bladder.

WEDNESDAY, 1:30–3 p.m.—Surgical Injuries of the Lower Urinary Tract.

THURSDAY, 9 a.m.–12 noon.—Surgical Forum Session.

FRIDAY, 1:30–3 p.m.—Management of Obstructions of the Upper Urinary Tract.

NEUROLOGIC SURGERY

THURSDAY, 9 a.m.–12 noon.—Surgical Forum Session.

FRIDAY, 9–10:30 a.m.—Surgical Management of Intracranial Aneurysms and Arteriovenous Malformations; 10:30 a.m.–12 noon.—Surgical Management of Cerebrovascular Disease; 1:30–4:15 p.m.—Neurosurgery Symposium.

ORTHOPEDIC SURGERY

WEDNESDAY, 2–5 p.m.—Orthopedic Surgical Forum Session.

FRIDAY, 1:30–3 p.m.—Fractures of Tarsal and Metatarsal Bones; 3:15–4:45 p.m.—Differential Diagnosis and Treatment of Low Back Pain and Sciatica.

PLASTIC SURGERY

THURSDAY, 9 a.m.–12 noon.—Plastic Surgical Forum Session.

FRIDAY, 1:30–3 p.m.—Reconstructive Surgery of the Neck; 3:15–4:45 p.m.—Reconstructive Surgery of the Eyelids and Orbital Region.

THORACIC SURGERY

FRIDAY, 1:30–3 p.m.—Selective Pulmonary Resection; 3:15–4:45 p.m.—Recent Developments in Cardiac Surgery.

Ophthalmology and Otolaryngology

Ophthalmology and otolaryngology will have one session each, instead of the usual three-day sessions. The decision to have one session each was reached by the respective Advisory Councils because annual meetings of the American Boards of Ophthalmology and Otolaryngology, and Academy meetings of these two specialties are being held during and immediately following Congress week.

Postgraduate Courses

The popularity of the postgraduate courses increases. Each year attendance grows, and tickets for these classes are greatly in demand. Eight postgraduate courses will be offered, including four in general surgery. All classes will meet Monday through Thursday mornings from 8:30 to 11:30 with one exception: the course in Obstetrics and Gynecology will be given Monday through Friday. Courses and Chairmen follow:

1. Preoperative and Postoperative Care. HENRY THOMAS RANDALL, New York.
2. Gastrointestinal Tract. WILLIAM P. LONGMIRE, JR., Los Angeles.
3. Diseases of the Liver, Biliary Tract, and Pancreas. J. ENGLEBERT DUNPHY, Boston.
4. Cardiovascular Surgery. F. A. SIMEONE, Cleveland.
5. Fractures and Dislocations. FLOYD H. JERGESON, San Francisco.
6. Gynecology and Obstetrics. PHILIP ARNOT, San Francisco.
7. Orthopedic Surgery. FREDERIC C. BOST, San Francisco.
8. Surgical Aspects of Pulmonary Disease. PAUL C. SAMSON, Oakland.

Forum on Fundamental Surgical Problems

Dr. Harris B. Shumacker, Jr., Indianapolis, Chairman, and the Forum Committee believe this now-famous Forum on original research will be extremely interesting this year. Morning and afternoon sessions are scheduled throughout the week, with 16 sessions in all. The general session on Friday at 9 a.m. entitled "What's New in Surgery?" will consist of reports by the presiding officers of six or more of the Surgical Forum sessions, summarizing the high-lights of research work reported in their Forum sessions.

Television, Ciné Clinics, Motion Pictures

Two-way television, with audience participation, proved phenomenally successful at last year's Congress in Chicago and will be repeated in San Francisco. Drs. H. Glenn Bell, San Francisco, and J. Garrott Allen, Chicago, are in charge of the television program, which will emanate from the H. C. Moffitt Hospital. Thirteen operations are scheduled, mornings and afternoons during the week. Ciné clinics and the motion picture program are directed by the College's Committee on Motion Pictures, under the chairmanship of Dr. Hilger Perry Jenkins, Chicago. Emphasis is on subject matter this year, and doctors from Canada and the United States are participating in what promises to be the best film program presented to date. All films are first reviewed by the Committee. The popular Motion Picture Symposium will again be held on Wednesday evening.

Medical Students as Congress Guests

The Board of Regents has approved a plan whereby medical students will take part in forthcoming Congresses for the next three years at the expense of the College. Representative students from one-third of the approved medical schools in Canada and the United States will be invited to each Congress, with schools participating in rotation according to the geographic location of the Congress. However, medical schools within the host city will not be invited to participate in the Congress held in that city, but will instead send a student representative to a future Congress held in another city.

Deans of approved medical schools have collaborated in planning this program, hailing this College project as a valuable contribution to the professional education of the student. Sixteen medical schools will send student representatives to the San Francisco Clinical Congress. Only third-year students are eligible, and the one student from each school will be selected by vote of his classmates.

Scientific and Technical Exhibits

Forms to be used in applying for scientific exhibit space may be obtained from Dr. George W. Stephenson, 40 East Erie Street, Chicago 11, Illinois. After July 1 no application will be accepted. The Technical Exhibition is under the direction of Thomas E. McGinnis, Assistant Business Manager for the Clinical Congress, and inquiries may be directed to him at the same address.

Advance Registration

Advance registration forms for the Congress —hotel, postgraduate courses, travel—will be mailed to Fellows early in June, and to non-Fellows some time later. This step is being taken because hundreds of requests are received from non-Fellows who wish to attend this meeting, and the College feels that it is only fair to give Fellows the first choice in accommodations. Hence, Fellows are strongly urged to take advantage of this consideration, returning their forms as soon as possible.

In addition to the advantage listed above, anyone registering in advance will find his badge waiting for him upon arrival at the Congress, and avoid waiting in line to register.

Anyone unable to register in advance may present his credentials at the Central Registration Desk. Hours there will be as follows: Sunday, October 7, from 3 to 7 p.m.; Monday, October 8, 8 a.m. to 5:30 p.m.; Tuesday through Friday, 8 a.m. to 5 p.m.

Fellows whose dues are paid to December 31, 1955, pay no registration fee, but those whose dues are not paid are assessed $20.00. Non-Fellows also pay $20.00 and members of the Federal services $10.00. No registration fee is required of Initiates, Candidates, or Surgical Residents. Everyone who attends a postgraduate course pays the $5.00 fee for the course. It is suggested that non-Fellows bring medical identification with them in order to simplify their registration.

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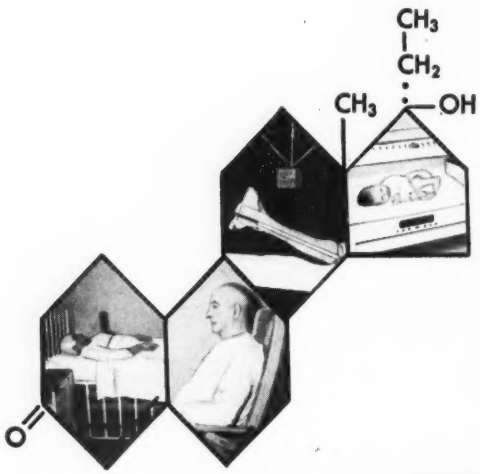

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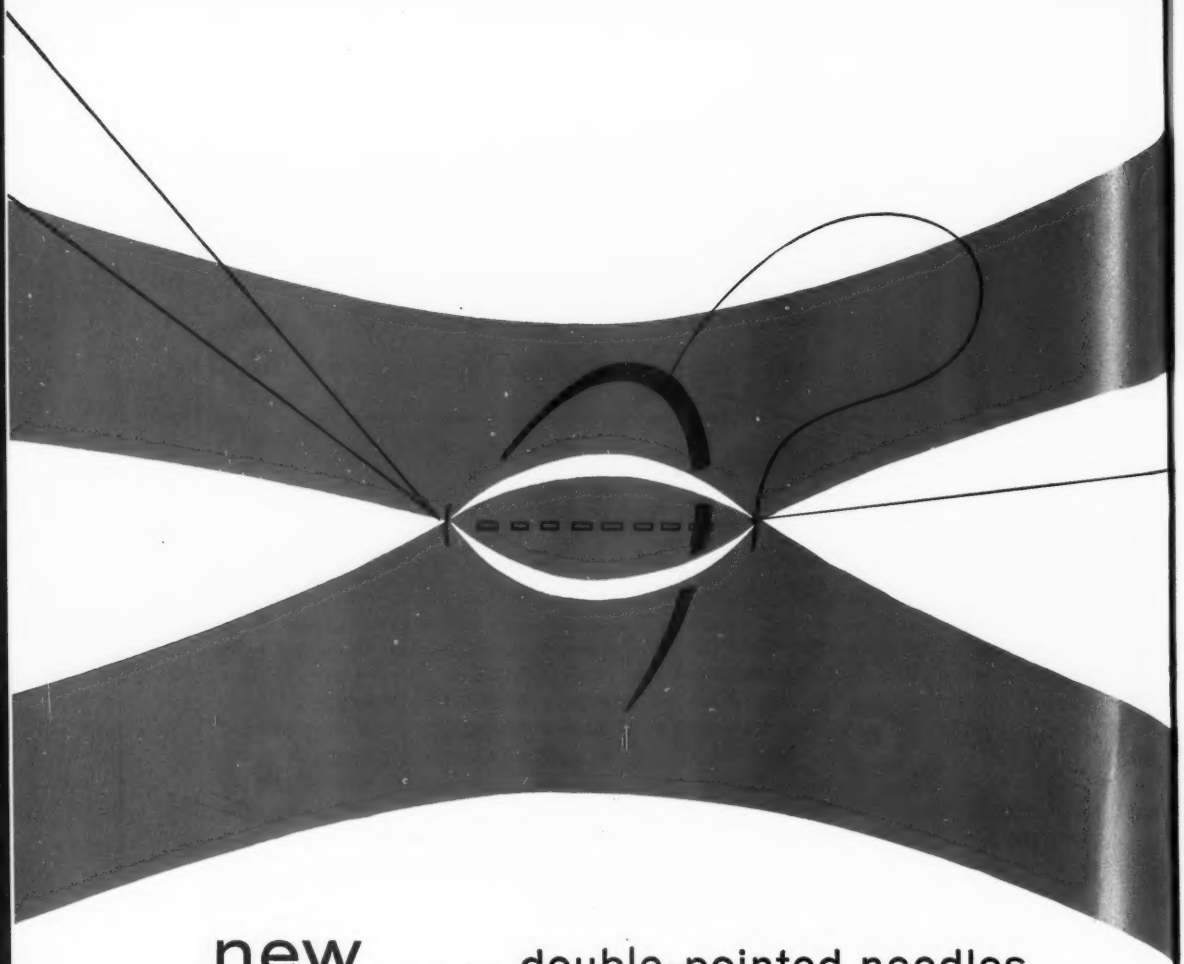

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(1) Jennings, E. R., and Cowley, R. A.: Surgery 37:206, 1955. (2) Lam, C. R., in Lam, C. R.: Cardiovascular Surgery, Philadelphia, W. B. Saunders Company, 1955, p. 355.

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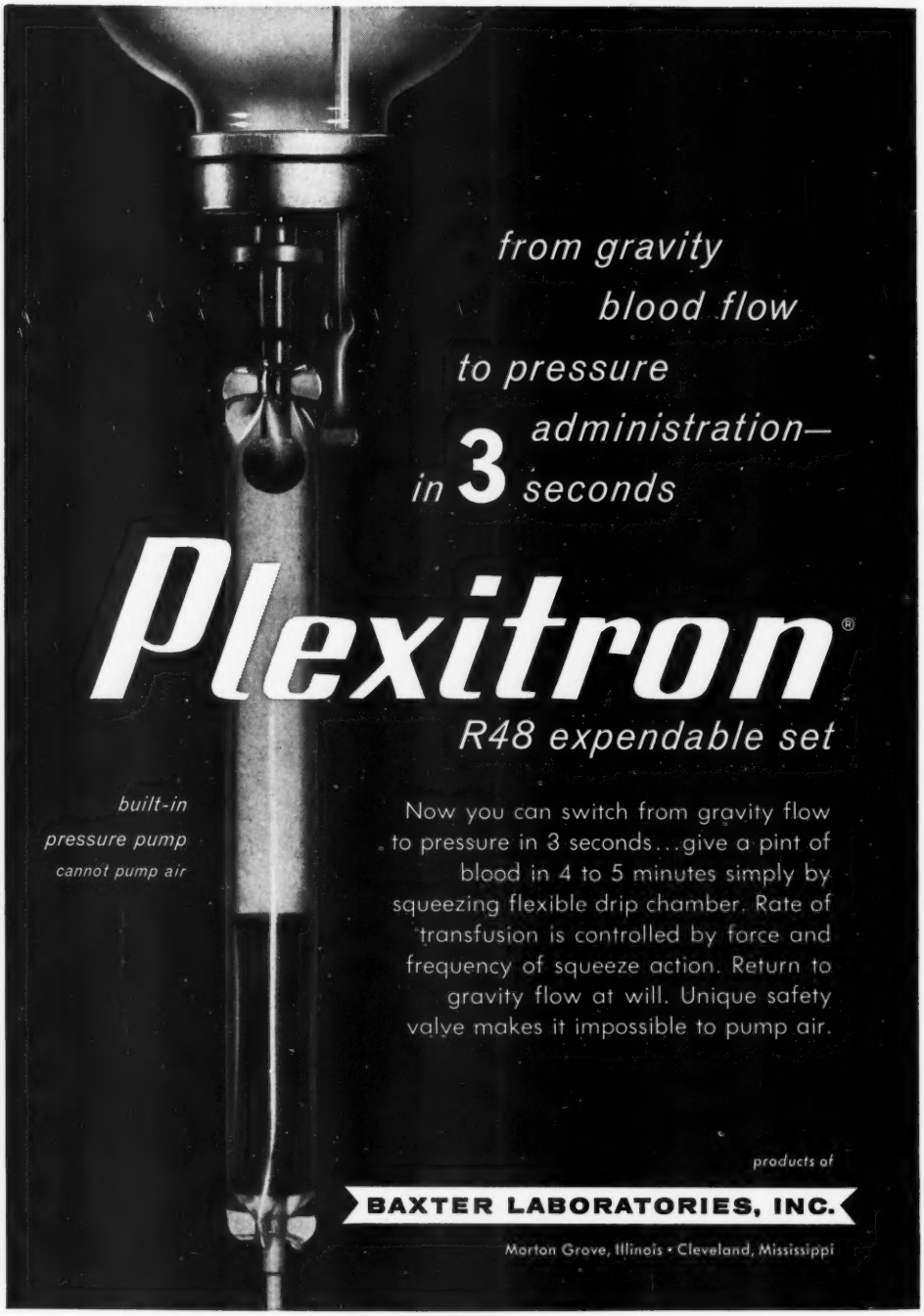
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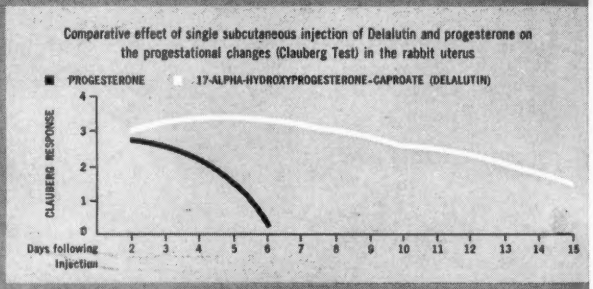
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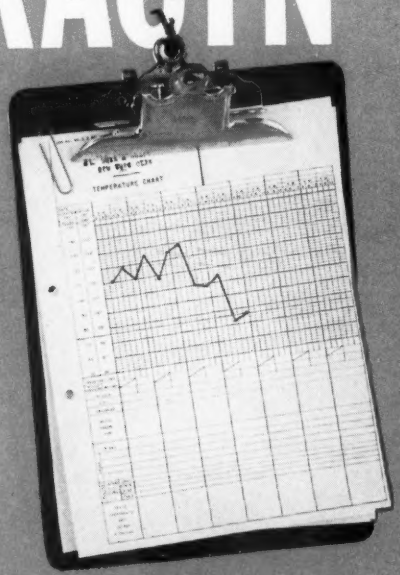

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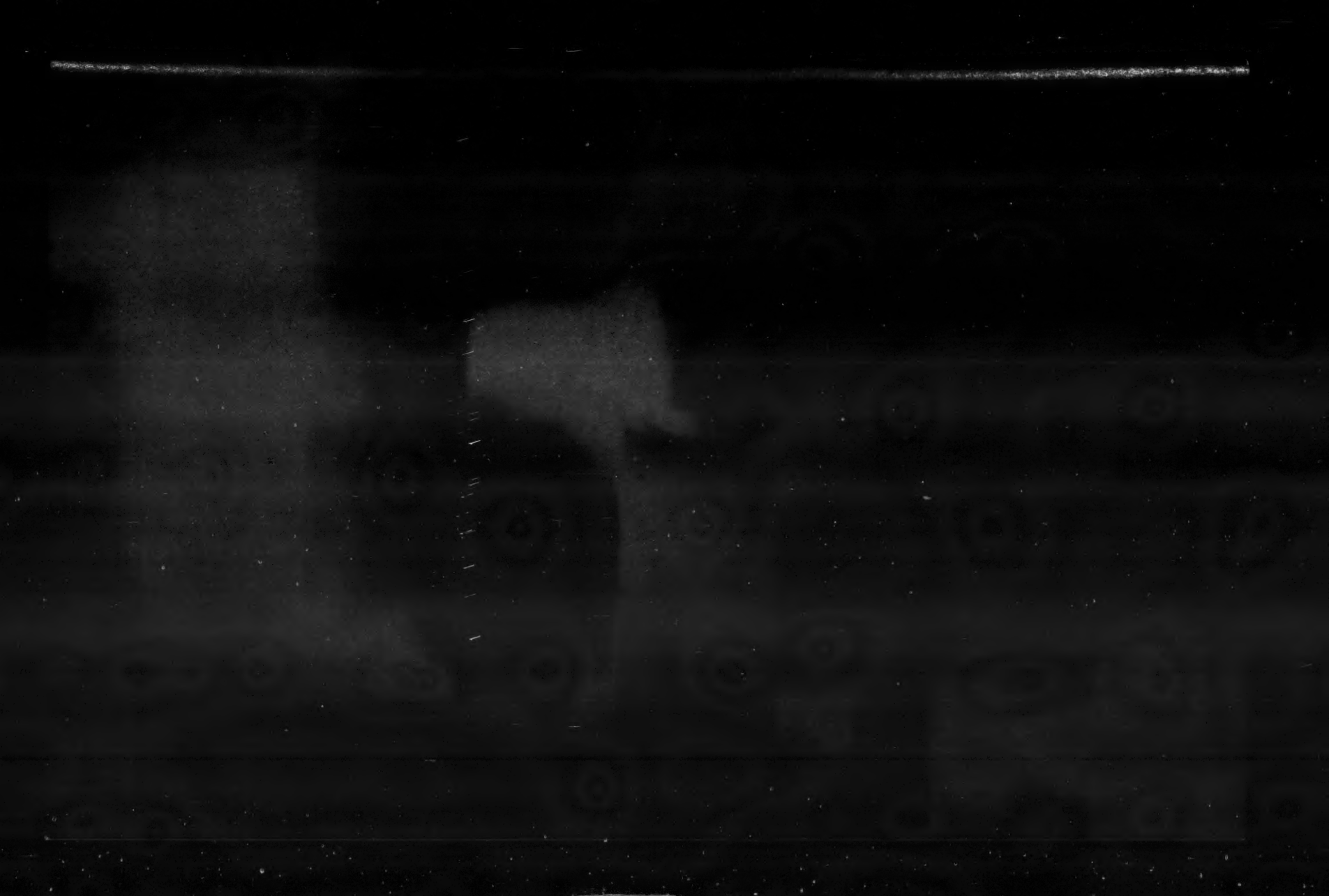

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References: 1. N.N.R. 1954, p. 107. 2. J.A.M.A. 153:1516 (Dec. 26) 1953.

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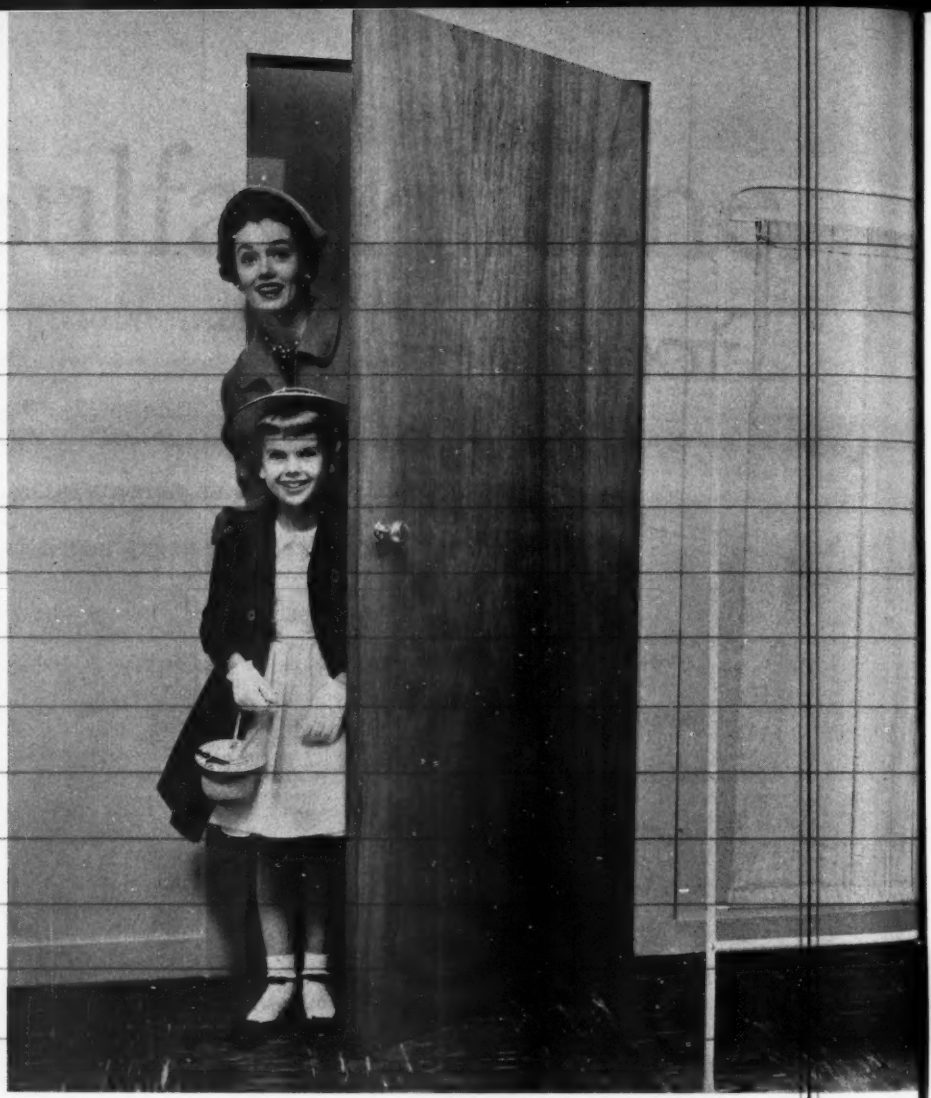

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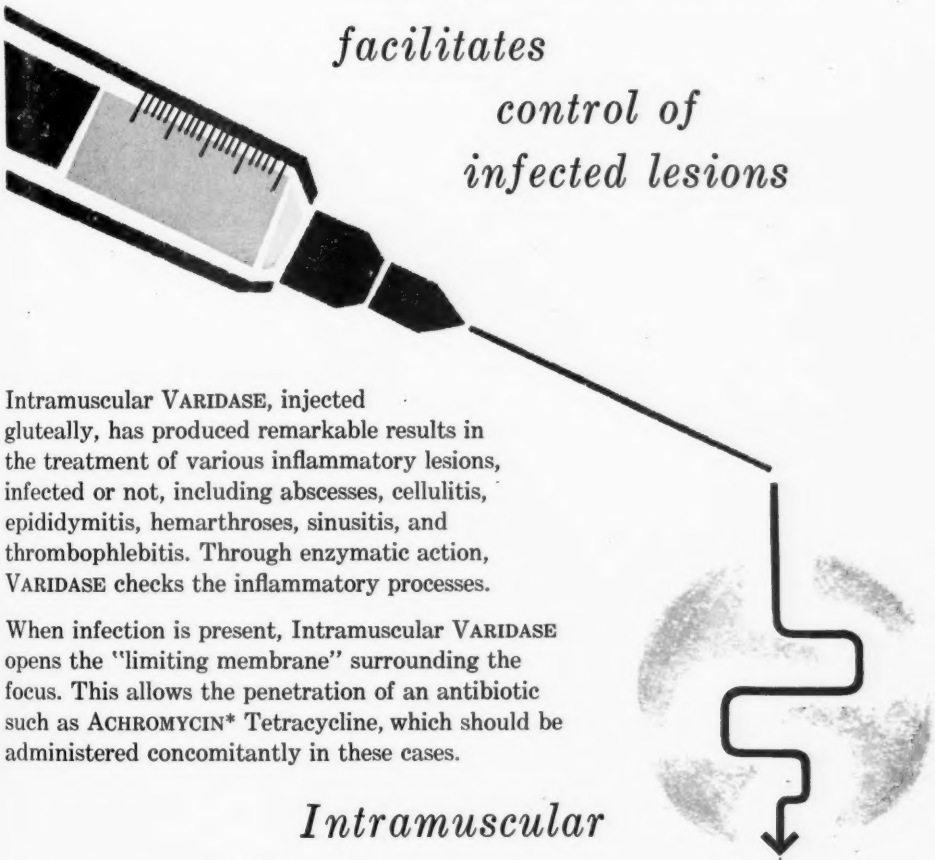

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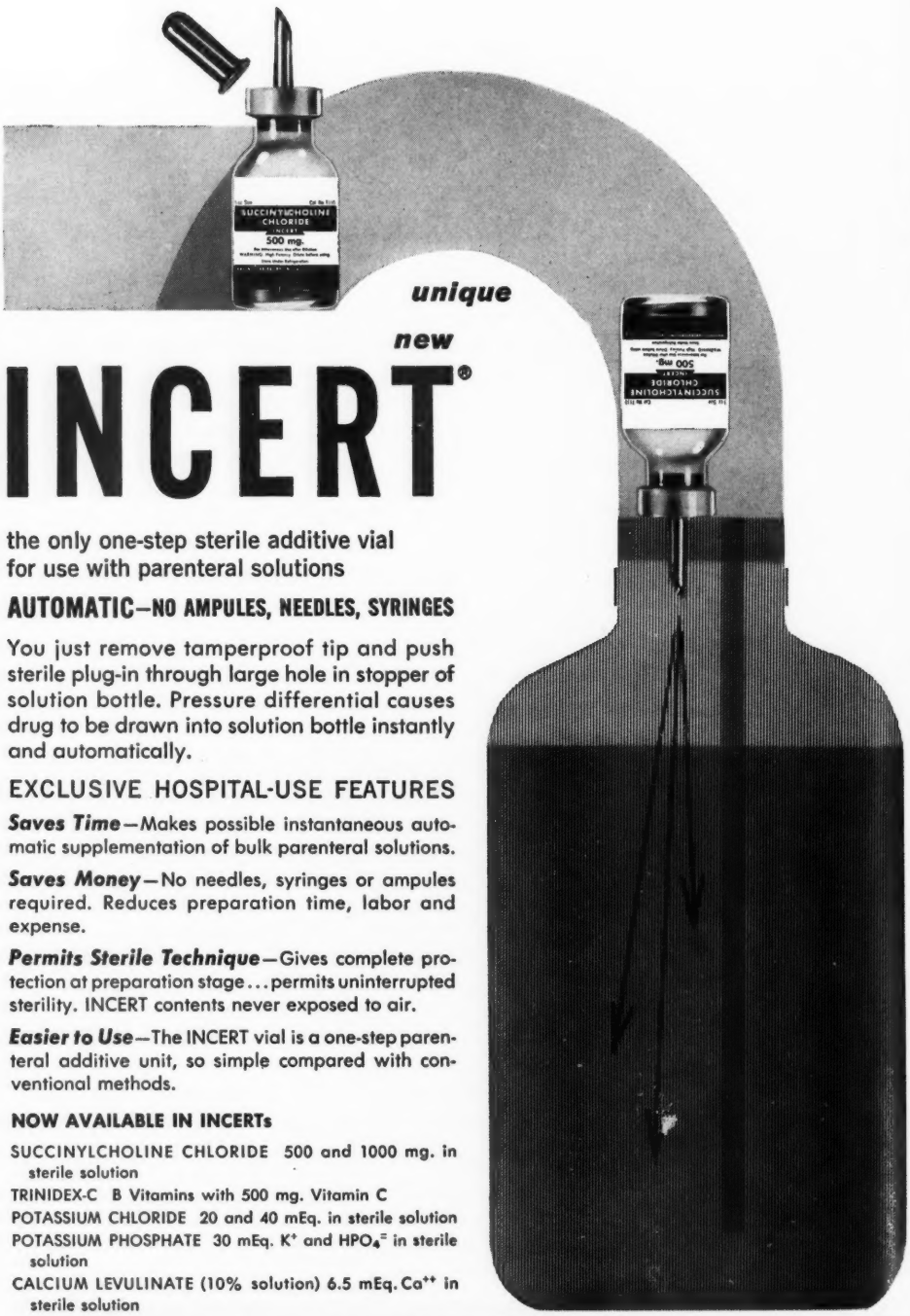

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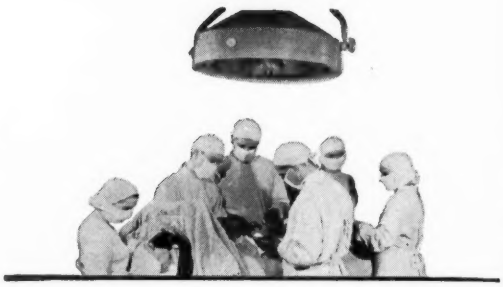

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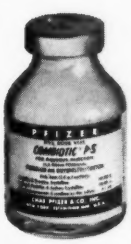

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1. Doyle, J. C.: Urol. & Cutan. Rev. *55*:618 (Oct.) 1951. • 2. Hamblen, E. C., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657. • 3. Doyle, J. C.: California Med. *71*:15 (July) 1949.

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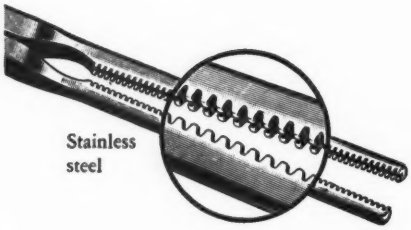

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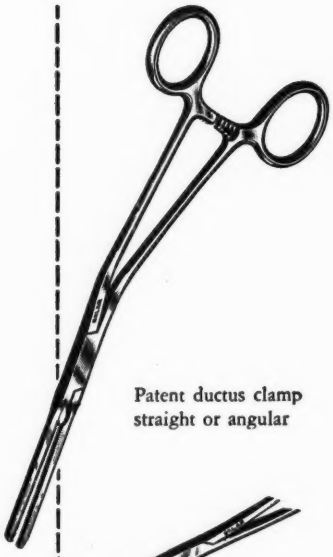
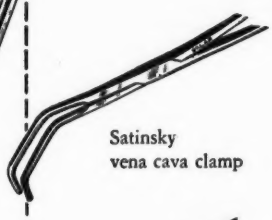
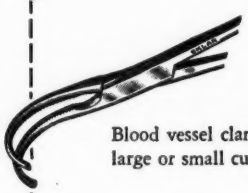


Patent ductus clamp
straight or angular



Satinsky
vena cava clamp



Blood vessel clamp
large or small curve

Coarctation clamp
straight or angular

Bronchus clamp, angular

Bulldog clamp
2", 2½" 3", 3½"

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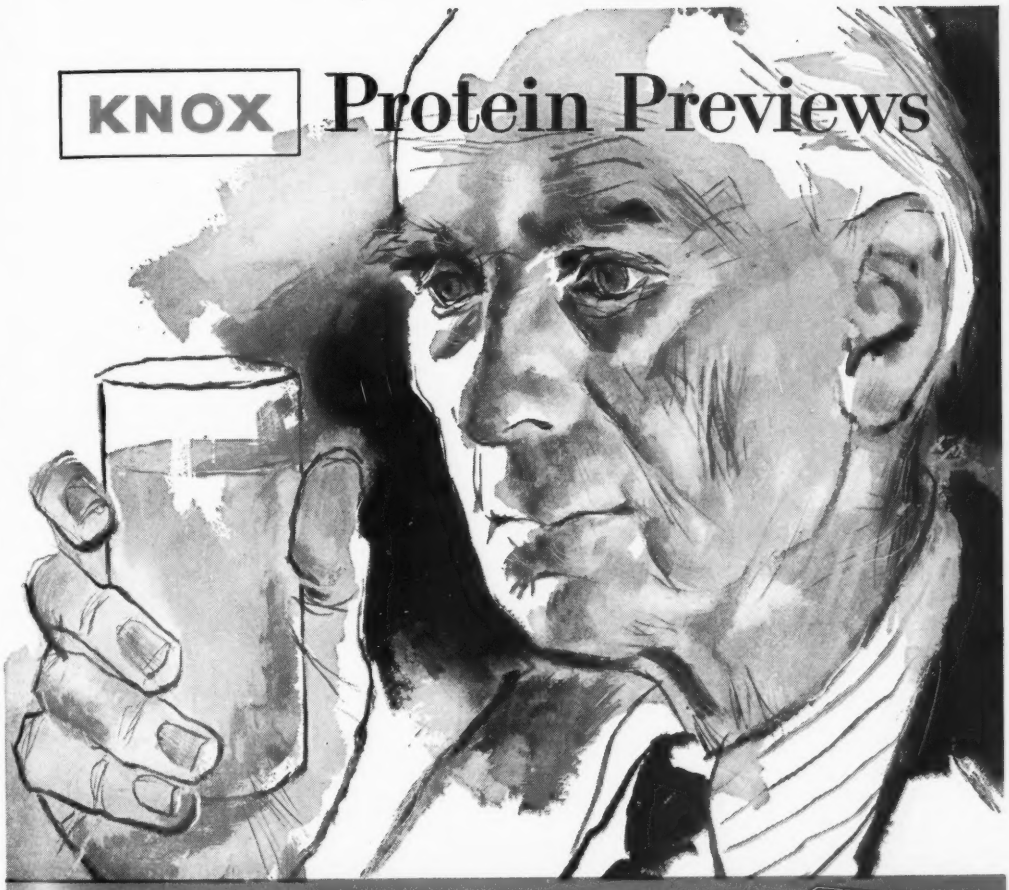

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9/12/55

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*Communication to Abbott Laboratories

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Adults: one green 60 mg. capsule daily or one to three orange 20 mg. capsules daily.

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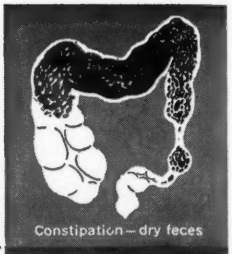
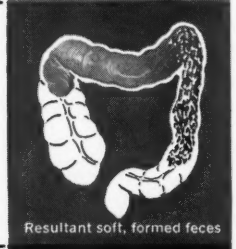
1. Spiesman, M. C., and Malow, L.: Journal-Lancet (June) 1956.
2. Antos, R. J.: Southwestern Med. *37*:236 (April) 1956.
3. Wilson, J. L., and Dickinson, D. G.: J.A.M.A. *158*:261 (May 28) 1955.

Permits normal bowel habits



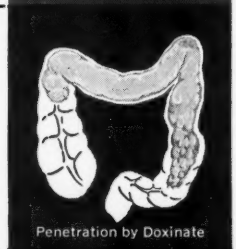
Constipation—dry feces

Effective



Resultant soft, formed feces

Gradual action



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Nontoxic

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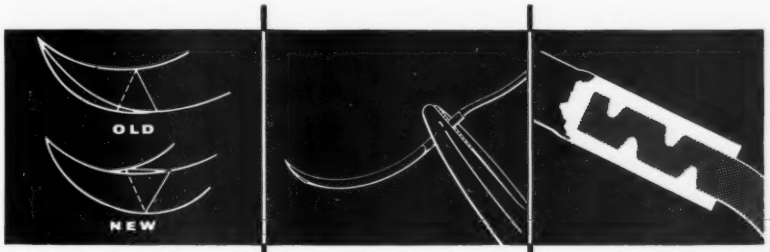

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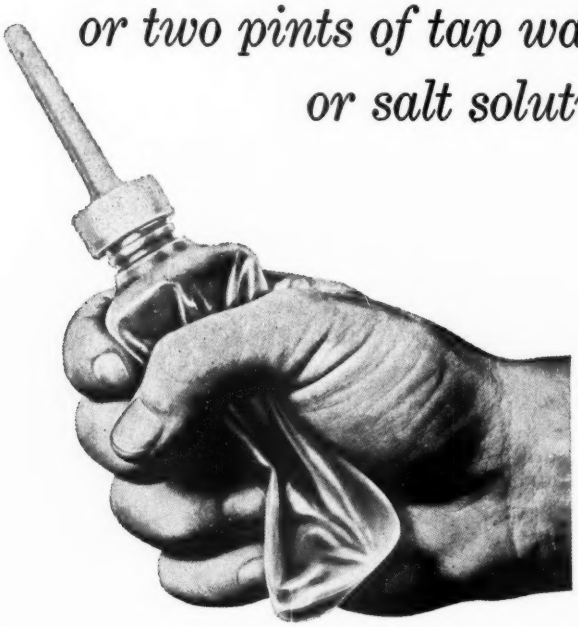

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The Use of the Systemic Hemostat Carbazochrome Salicylate

J. C. Bacala, M.D.

(Abstracted from the Western Journal of Surgery, Obstetrics, and Gynecology, 64:88 (1956)

The author emphasizes the need for dependable chemical control of bleeding and oozing, and reviews the methods that have been tried to attain hemostasis, including the use of vitamin K and bioflavonoids.

He gives the history of carbazochrome salicylate and describes the clinical work completed to demonstrate its effectiveness. It appears to be specific for conditions characterized by increased capillary permeability. It has no effect on large blood vessels; it does not alter blood components; it does not affect blood pressure or cardiac rate. It has neither vasoconstrictor or vasodilator action. The drug has no known contraindications.

He reviews 1051 cases from the files of St. Anthony Hospital, Louisville, Kentucky, of which 330 were treated with Adrenosem Salicylate. 317 were surgical cases and 13 obstetric-gynecological conditions. The treatment was given for symptomatic relief, and as a clinical recourse for patient safety.

In 1015 tonsillectomy patients the following results were noted: There was bleeding in 85 (19.8%) of 429 patients who received no medication. Patients who received a compound of oxalic and malonic acids numbered 115. Of these 16 (14%), developed bleeding. Of 248 patients receiving vitamin K preparations, 47 (19%) had postoperative hemorrhage. 233 patients received Adrenosem Salicylate. Of this group, only 16 (7%) had bleeding.

In other surgical conditions, Adrenosem was used successfully in gastrointestinal bleeding, cataract extraction, incisional seepage, and transurethral prostatectomy. It was also effective in 12 cases of epistaxis.

In the field of obstetrics and gynecology, Adrenosem controlled bleeding in menometrorrhagia, hymeneal laceration, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and in two cases of surgery during pregnancy.

The author points out that in pregnancy, seepage bleeding occurs more because of capillary permeability, and in spite of increased coagulability. Here, Adrenosem becomes specific for strengthening capillary resistance.

Many of the observations in this study, however, involved bleeding incident to trauma of incision, retraction, dissection, tearing and stretching. In these conditions, he reasons that Adrenosem causes hemostasis by its effect on the capillary intercellular cement substance so that the cells draw closer together, and the ends of the capillaries constrict, causing a "self-clamping" mechanism.

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1. Carroll, J.J., and Hudson, P.W.: Canad. Anaes. Soc. J. *2*:340 (Oct.) 1955.

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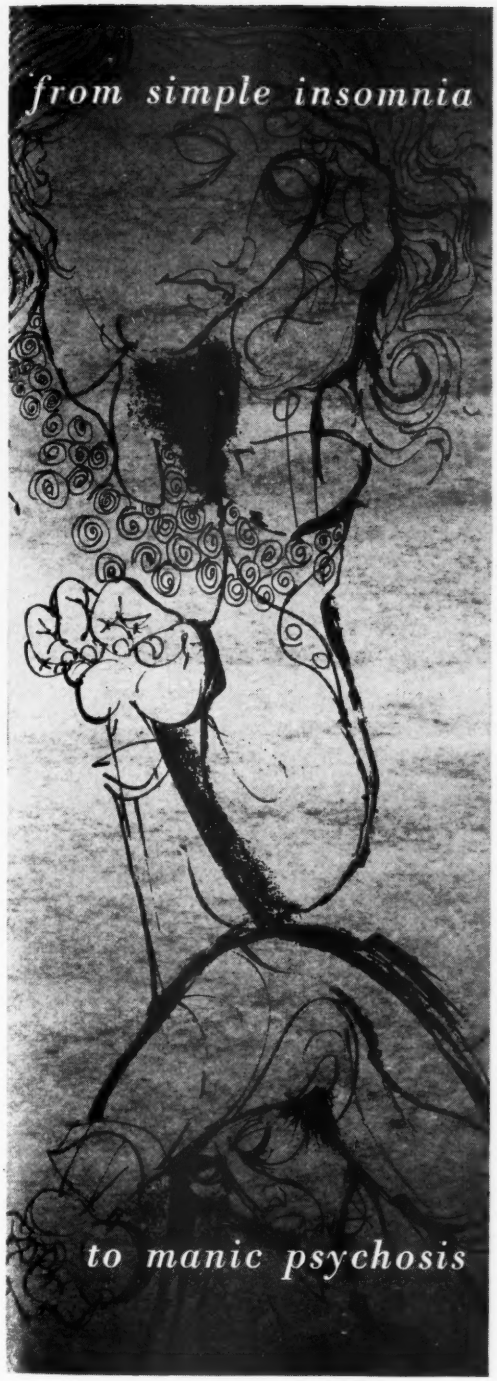

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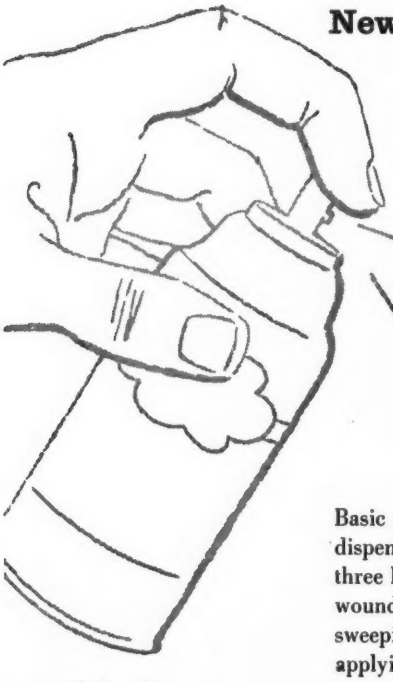

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1. Vibesate (Aeroplast), New and Nonofficial Remedies, 1955, p. 541.
2. Choy, D.S.J.: A.M.A. Arch. Surg. 68:33 (Jan.) 1954.
3. Rigler, S. P., and Adams, W. E.: Surgery 36:792 (Oct.) 1954.
4. Wexler, D. J., Bromberg, F., Rakieten, M. L., and Ryan, B. J.: Am. J. Surg. In Press.

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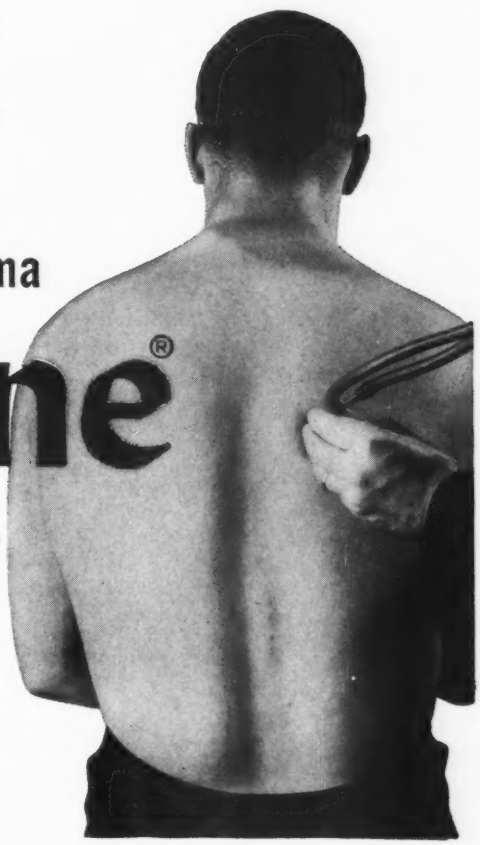

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1. Johnston, T. G., and Cazort, A. G.: J. Allergy 27:90, 1956. 2. Schwartz, E.: New York J. Med. 56:570, 1956. 3. Schiller, I. W., et al.: J. Allergy 27:96, 1956.

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*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, ed. 2, New York, The Blakiston Company, Inc., 1954, chap. 98, pp. 702, 703.

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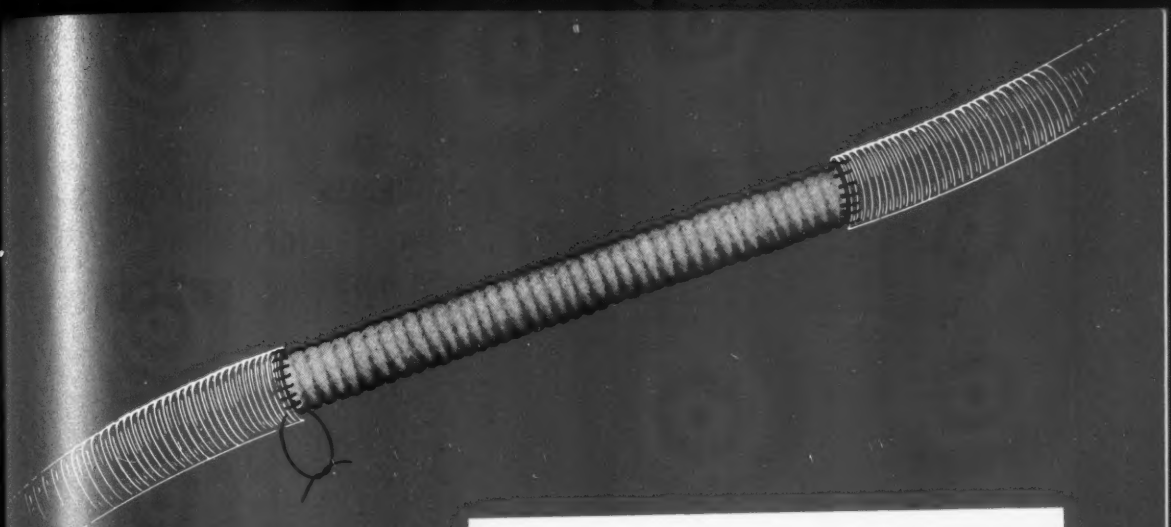

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Reference: Edwards, W. Sterling and Tapp, James S.: Chemically Treated Nylon Tubes as Arterial Grafts, Surgery 38: 61-70; 89-91 (July) 1955.
Edwards, W. Sterling and Tapp, James S.: Peripheral Artery Replacement with Chemically Treated Nylon Tubes, Surg., Gynec. & Obst. 102: 443-449 (April) 1956.

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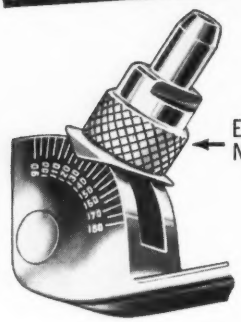

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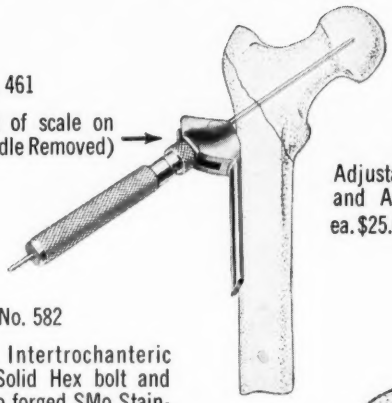

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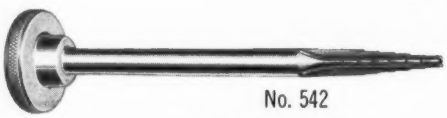

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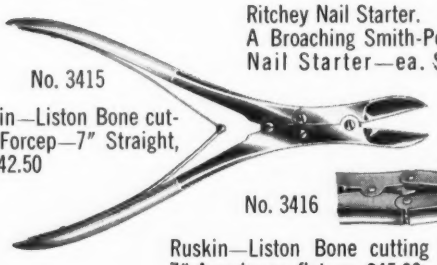

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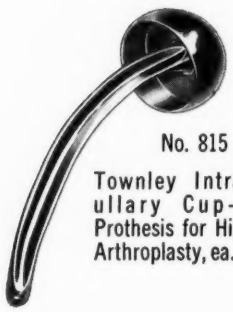

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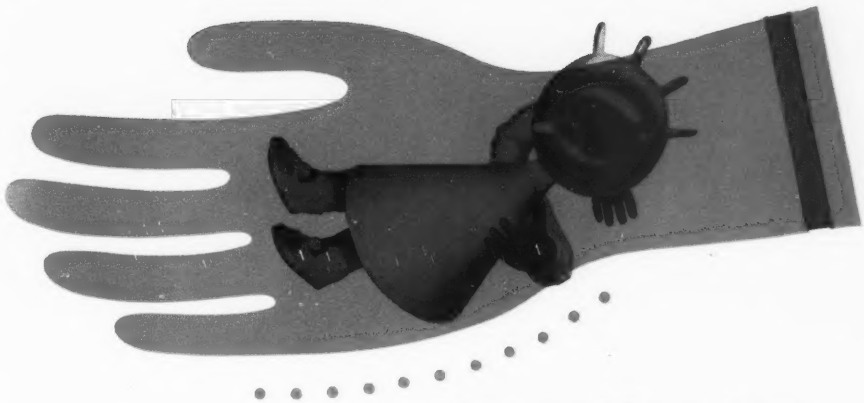

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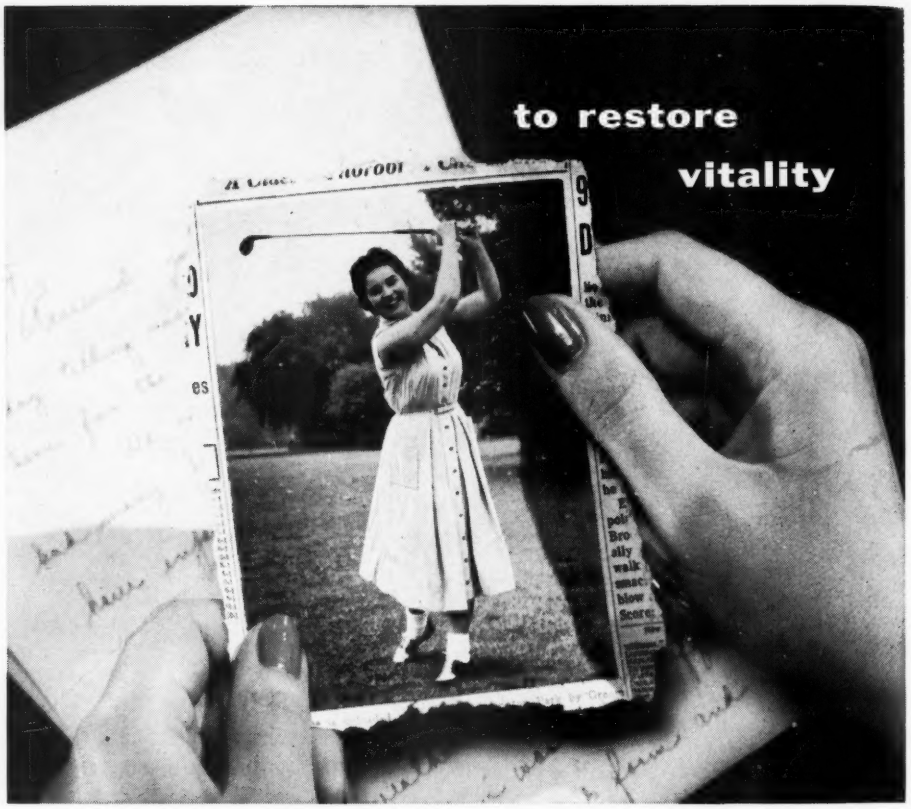

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1. Cross, Frederick S., M.D.: Clinical Medicine, 1121-1125, November, 1955.
2. Hosler, Robert M., M.D., Cleveland, Ohio: A Manual on Cardiac Resuscitation, Charles C. Thomas—publisher, 1954.

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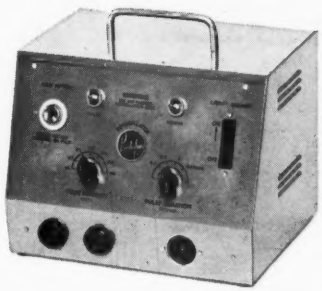

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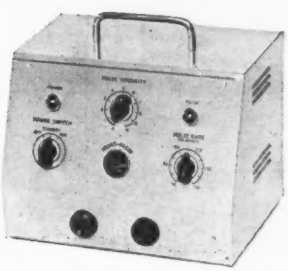

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[1]Albertson, H.A. and Trout, H. H., Jr.: *Antibiotics Annual* 1954-55, Medical Encyclopedia, Inc., New York, N.Y., 1955, pp. 599-602.

[2]Prigot, A.; Whitaker, J. C.; Shidlovsky, B. A., and Marmell, M.: *ibid*, pp. 603-607.

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NUTRIENTS	OATMEAL	MILK	TOTAL	NUTRIENTS	OATMEAL	MILK	TOTAL
†Protein	4.7 Gm.	3.9 Gm.	8.6 Gm.	†Iron	1.28 mg.	0.12 mg.	1.40 mg.
Carbohydrate	17.7 Gm.	5.7 Gm.	23.4 Gm.	†Calcium	15 mg.	148 mg.	163 mg.
Fat	2.0 Gm.	4.4 Gm.	6.4 Gm.	†Phosphorus	115 mg.	113 mg.	228 mg.
†Thiamine	0.18 mg.	0.05 mg.	0.23 mg.	Potassium	162 mg.	163 mg.	325 mg.
†Niacin	0.26 mg.	0.10 mg.	0.36 mg.	Zinc	1.08 mg.	0.45 mg.	1.53 mg.
†Riboflavin	0.05 mg.	0.19 mg.	0.24 mg.	†Folic acid	11.4 mcg.	0.3 mcg.	11.7 mcg.
†Pyridoxine	0.07 mg.	0.06 mg.	0.13 mg.	Vitamin B_{12}	0.1 mcg.	0.7 mcg.	0.8 mcg.
Pantothenic acid	0.25 mg.	0.41 mg.	0.66 mg.	†Copper	0.31 mg.	0.04 mg.	0.35 mg.
†Vitamin A plus Carotenoids	—	0.08 mg.	0.08 mg.	Manganese	1.45 mg.	0.002 mg.	1.45 mg.
Magnesium	51 mg.	14 mg.	65 mg.	†Calories	111	81	192

*1 oz. oatmeal (dry), 4 oz. whole milk; usually-added sugar not included in evaluation; sources supplied on request.

†Nutrients for which Daily Dietary Allowances are recommended by the National Research Council.

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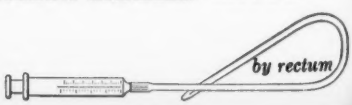
Your young patient is spared the nightmare of the operating room with PENTOTHAL Sodium administered rectally. He goes to sleep in his own bed, awakens there with complete amnesia of events between.

And, because Rectal PENTOTHAL reduces the dosage of inhalation and supplementary agents, after-effects are markedly lessened. As a basal anesthetic, or as a sole agent in minor procedures, PENTOTHAL by rectum affords a notably safe and simple approach to pediatric anesthesia. Abbott

PENTOTHAL® Sodium

(Thiopental Sodium, Abbott)



in rheumatoid arthritis

continuing benefits

for successful corticosteroid therapy

METICORTELONE*

(PREDNISOLONE)

- therapy usually undisturbed by sodium retention, edema, weight gain
- excellent relief of arthritic pain, swelling, tenderness
- spares patients salt-poor diets
- up to 5 times as potent as hydrocortisone

Available as 1, 2.5, and 5 mg. tablets

METICORTELONE,* brand of prednisolone. *T. M. KL-J-66-256

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Deserve Your Complete Confidence

PIONEER ROLLPRUFS

UNTREATED SURGICAL GLOVE

● *Since May, 1952 Processed To Prevent the Ozone Cracking Common To Many Surgical Gloves. Insist on Rollprufs because they stay safe longer.*

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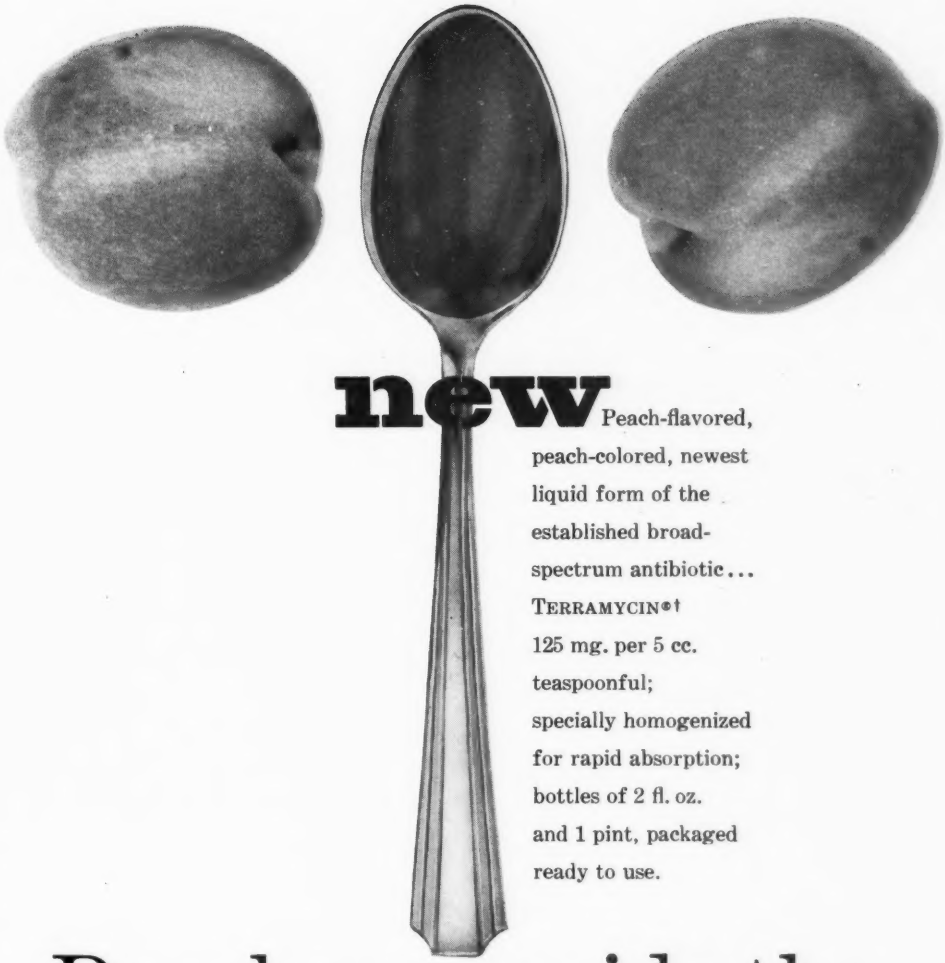
386 Tiffin Road, Willard, Ohio, U.S.A.

Pioneers in Surgical Glove Improvement for over 35 Years



new Peach-flavored, peach-colored, newest liquid form of the established broad-spectrum antibiotic... TERRAMYCIN®† 125 mg. per 5 cc. teaspoonful; specially homogenized for rapid absorption; bottles of 2 fl. oz. and 1 pint, packaged ready to use.

Peaches provide the delightful new taste in TERRABON*

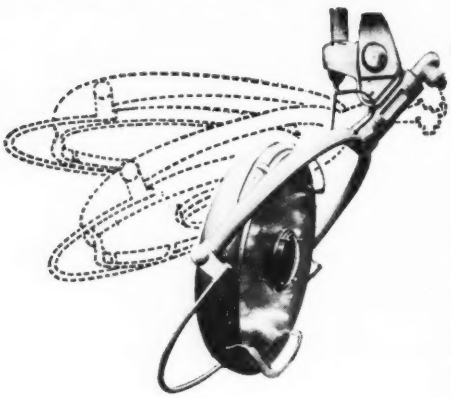
BRAND OF OXYTETRACYCLINE

HOMOGENIZED MIXTURE

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y. Pfizer

*Trademark †Brand of oxytetracycline

ONLY *Castle* "60 SERIES" LIGHTS



. . . GIVE TOTAL HEMISPHERIC MANEUVERABILITY

"FLOATING" OFFSET SUSPENSION INSURES EFFORTLESS, INSTANT RE-POSITIONING WITHOUT TRACKS OR HAZARDOUS COUNTERWEIGHTS

IN VERTICAL PLANE — cam-balanced lamphead "floats" up and down at finger touch, but it is rarely necessary to adjust lamphead. The Castle light is in perfect focus 30 to 60 inches from the source!

IN TRUE HORIZONTAL PLANE - lamphead descends, pivots fully to illuminate gynecologic or perineal procedures. Five reflectors flood field with soft radiance at surgeon's touch of sterile control handles. Unprecedented deep cavity penetration is without glare or shadow.

IN LATERAL ANGULATION - lamphead swings effortlessly in full 8′ 3″ circle. May be centered under suspension, or directed obliquely from side and end table positions without crowding team. Vital for kidney, radical mastectomy, intratracheal procedures, thoracic, orthopedic, suprapubic and allied approaches.

INSTANT COLOR PHOTOGRAPHY. . . *AS IT HAPPENS!*

For emergency photography, Castle's new COLOR CAMERA ATTACHMENT is recessed in lamphead in place of Center Spotlight. Holds pre-set Kodak 35mm camera. 20 or 36 exposures without reloading. Film advanced, shutter tripped remotely. Range-finder spotlights for perfect focusing. No flash bulbs required.

WRITE TODAY for complete specifications on Models 61, 62 and 63, and details of Color Camera Attachment.

Castle LIGHTS and STERILIZERS

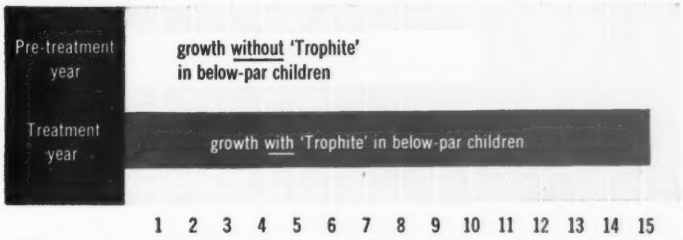
WILMOT CASTLE COMPANY

1809 E. Henrietta Rd. Rochester, N. Y.

for the child
who "just won't eat"

In a one-year, controlled study of children with secondary growth failure or clinical malnutrition, 'Trophite'—high dosage of B_{12} and B_1—increased growth by nearly 50% (see graph below).

AVERAGE GROWTH AND DEVELOPMENT RATE—LEVELS/YEAR


Pre-treatment year
growth without 'Trophite' in below-par children
Treatment year
growth with 'Trophite' in below-par children
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

(These levels represent growth in terms of both height and weight according to Wetzel's Grid technique.)

Try 'Trophite' in the child who "just won't eat." Both you and his parents will be delighted with his new appetite.

'Trophite' is available both as a truly delicious liquid and as tablets. Each teaspoonful (5 cc.) or tablet supplies: 25 mcg. B_{12}, 10 mg. B_1.

the high potency combination of B_{12} and B_1

Trophite* *for* appetite

*T.M. Reg. U.S. Pat. Off. *Smith, Kline & French Laboratories, Philadelphia*

new

Against Pathogen & Pain

in urinary tract infections

Azo Gantrisin combines the single, soluble sulfonamide, Gantrisin, with a time-tested urinary analgesic - in a single tablet.

Prompt relief of pain and other discomfort is provided together with the wide-spectrum antibacterial effectiveness of Gantrisin which achieves both high urinary and plasma levels so important in both ascending and descending urinary tract infections.

Each Azo Gantrisin tablet contains 0.5 Gm Gantrisin 'Roche' plus 50 mg phenylazo-diamino-pyridine HCl. Gantrisin® - brand of sulfisoxazole

ROCHE

Original Research in Medicine and Chemistry

EMULSION OF

Mephyton®

(VITAMIN K_1, MERCK)

Preferred product for routinely stabilizing prothrombin levels before surgery

MAJOR ADVANTAGES: Action detectable within 15 minutes; complete reversal of hypoprothrombinemia within 4-12 hours.

There are three significant reasons for preferring MEPHYTON over the menadione derivatives. The action of MEPHYTON is: (1) more rapid, (2) more complete, and (3) more prolonged. These advantages apply to either simple vitamin K deficiency states or in anticoagulant-induced hypoprothrombinemia. In the latter condition, MEPHYTON provides the *most* dependable and practical means of restoring normal levels of prothrombin.

INDICATIONS: Hypoprothrombinemia due to Dicumarol®, Cumopyran®, Hedulin®, Tromexan®, antibiotics, salicylates, obstructive jaundice, hepatic disease, impaired gastrointestinal absorption, and deficiency of vitamin K in the newborn.

SUPPLIED: In boxes of six 1-cc. ampuls, each cc. containing 50 mg. of vitamin K_1.

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DIVISION OF MERCK & CO., INC.

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gloves

SEPTISOL®
with HEXACHLOROPHENE

ANTISEPTIC
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SOAP

Regular washing with SEPTISOL forms an invisible but protective film on the skin, which through cumulative action keeps on killing bacteria—even many hours after washing—with complete skin safety.

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RESECTION OF MUCOCELE: Preoperative radiograph, A-P view

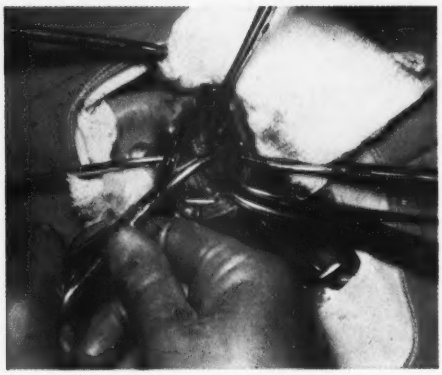
Radiography at work...*with color photography*

Preoperative photograph of patient. *See following page for additional steps in surgery.*

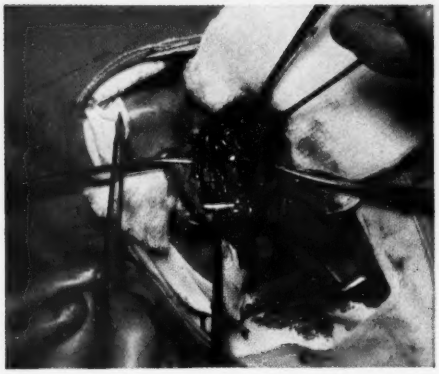
Here are radiography and photography working together to broaden the scope of medical knowledge, increase its usefulness.

With visual data such as shown, the physician has material for research and review, for teaching or discussion. Anytime he wishes, he can retrace steps in the treatment of the case—show the radiographs which helped him establish his diagnosis—show the steps in surgery or therapy, clearly, objectively.

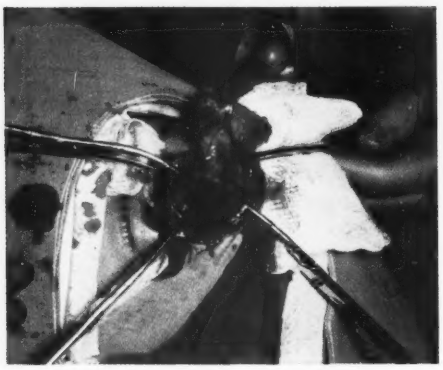
Kodak



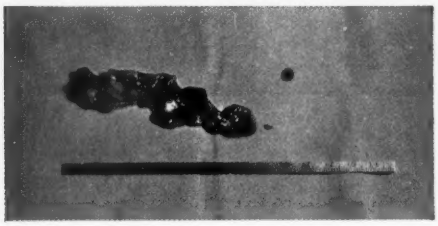
1. Removal of outer cortex of frontal sinus.



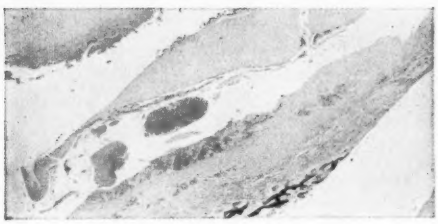
2. Frontal sinus cortex removed—*mucocele membrane* in evidence.



3. *Mucocele membrane* being removed from frontal sinus.

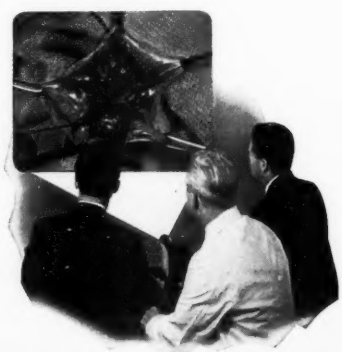


4. Portion of *mucocele.*



5. Photomicrograph of *mucocele membrane.* (Magnification, X10.)

For Radiography: Kodak Blue Brand X-ray Film and Kodak x-ray processing chemicals meet the most exacting requirements. They are always dependable—uniform. Quality-controlled—rigidly tested—they are *made to work together.*



For Color Photography: Kodachrome Film for miniature and motion-picture cameras;

Kodak Ektachrome Film and Kodak Ektacolor Film, Type B, for sheet-film cameras;

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Order x-ray products from your x-ray dealer, photographic products from your photographic dealer.

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The Name That Marks a New Era in Local Anesthesia

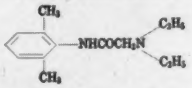
Xylocaine provides peak values in:

• **Duration** • **Clinical Effectiveness** • **Clinical Tolerance** • **Speed**
• **Stability** • **Versatility** • **Clinical Predictability** • **Safety** • **Depth**

Trade Name: XYLOCAINE **Generic Name:** lidocaine*

Chemical Name: α-Diethylaminoaceto-2,6-xylidide

Chemical Structure:



Potency: Two to three times that of procaine.

Duration of Action: Two to three times that of procaine.

Anesthetic Index: 1.8. **Surface Anesthetic Index:** 8.

Safety Factor: Two to three times that of procaine (because smaller concentrations and volumes are clinically as effective).

Sensitivity: Allergic manifestations and sensitizing reactions have never been reported.

Inhibition of Therapeutic Action of Sulfonamides or Antibiotics: None.

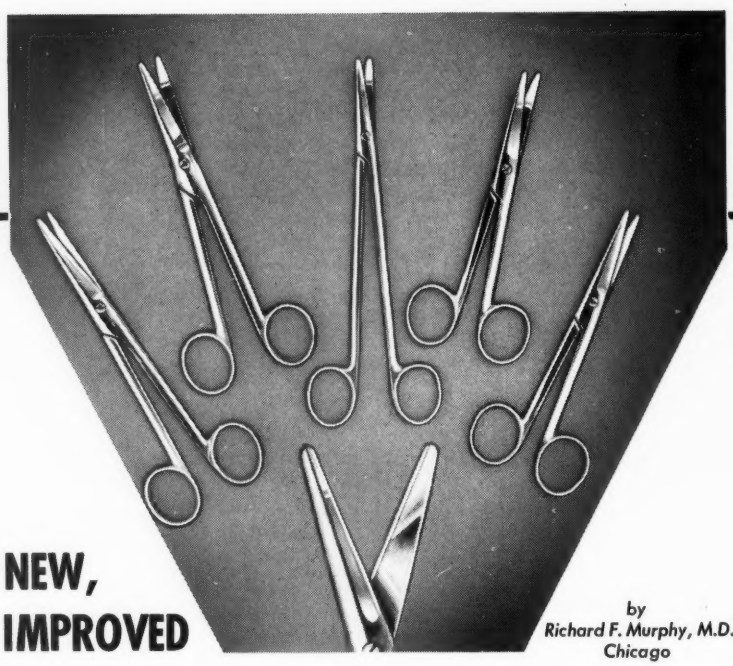
Versatility: Effective in local infiltration anesthesia; in major conduction anesthesia; in temporary therapeutic blocks for relief of pain; in topical anesthesia.

Available on Request: Descriptive literature, bibliography, and trial supply.

Supplied: Vials, 0.5%, 1% and 2% in 20 cc. and 50 cc. without and with epinephrine 1:100,000; 100 cc. vials, 1% without epinephrine. Ampoules, 2 cc., 2% without and with epinephrine 1:100,000.

Astra Pharmaceutical Products, Inc., Worcester 6, Mass.

*U. S. PATENT NO. 2,441,498



NEW, IMPROVED

by
Richard F. Murphy, M.D.
Chicago

R65 Dissecting Scissors With Sure-Cutting Tungsten Carbide Blades

These improved stainless steel scissors *with hard tungsten inserts as cutting edges* have proved highly successful. They are being used to cut fascia, peritoneum, muscle, scar tissue, cartilage, uterus, ligamentous tissue, silk and catgut suture materials. They have been washed and sterilized with other instruments and in the regular manner. Rough handling has failed to damage the cutting edges, and after hard usage the instruments remain as sharp as the day they were made. The tungsten edges are permanently bonded to the blades, and there is no nuisance of replacing blade edges.

See Armamentarium Vol. II, No. VI.

MO-1601—METZENBAUM Tonsil Scissors	Each	**$15.30**
In dozen lots, each		**12.75**
SU-1803—MAYO Dissecting, straight, 5½″ length, each		**14.25**
In dozen lots, each		**11.85**
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SU-1813—MAYO Dissecting, curved, 5½″ length, each		**15.30**
In dozen lots, each		**12.75**
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Armamentarium

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to help the depressed and anxiety-ridden housewife who is surrounded by a monotonous routine of daily problems, disappointments and responsibilities . . .

With 'Dexamyl' you can often help her to face her problems; help her to regain lost interests; help her to rediscover the zest and purpose in life. The normalizing effect of 'Dexamyl' is free of the dullness caused by many "anti-anxiety" agents alone, free of the excitation sometimes caused by stimulants alone. Her mood normalized, disturbing mental and physical symptoms often vanish.

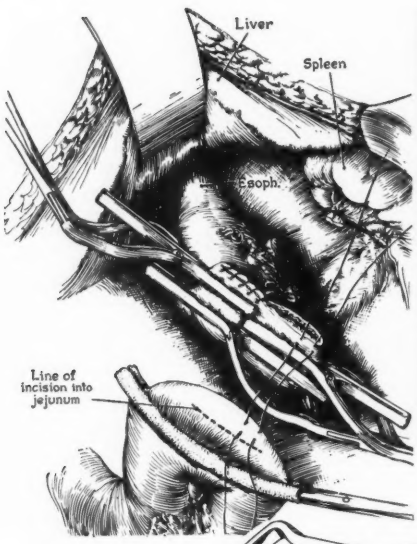
DEXAMYL* tablets · elixir · Spansule† capsules

smoothly and subtly relieves both anxiety and depression

Smith, Kline & French Laboratories, Philadelphia

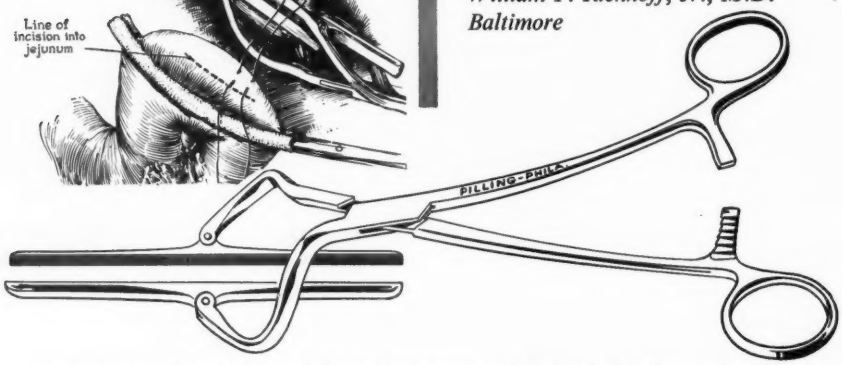
*T.M. Reg. U.S. Pat. Off.

†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.



RIENHOFF *ARTICULATED* ABDOMINAL CLAMP

Designed for
William F. Rienhoff, Jr., M.D.
Baltimore



A new stomach or intestinal clamp for a more refined technic of gastrectomy . . .

This clamp offers many advantages in gastrointestinal surgery:

- **Evenly Distributed Pressure**

Pressure is applied in the center of the blades —there is no scissors-like action.

- ***ATRAUMATIC**** **Blades**

Fine teeth provide firm hold on viscus, yet do not penetrate or traumatize wall of stomach or intestine. Non-crushing. Tissue between blades is in no way devitalized nor is the circulation jeopardized. Only the serosa is penetrated.

- **Positive Grip**

No gauze or rubber covering of the blades is necessary—*Atraumatic* jaws ensure positive grip—will not slip.

- **Versatile in Use**

Articulated Clamps may be applied for any type of partial or total gastrectomy desired. The angle of the handle affords an excellent tractor to be held by a second assistant.

- **Literature, "Technic of Use" is available.**

B2490—$65.00 f.o.b. Phila.—Price subject to change without notice.

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ers long life, sensitivity,
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surgery. Sheerer, softer,
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6 POWERED SURGICAL INSTRUMENTS AT THE SURGEON'S FINGER TIPS WITH Stryker Electro-Surgical Unit

One of a Series — THE STRYKER ROLO-DERMATOME

The Stand and Mayo Table is a convenient accessory. Hospitals may assure compliance with National Board of Fire Underwriter Standards for operating room safety by using the Stand which guarantees mounting of the motor above 5 ft.

Rolo-Dermatome $148.00

Because of the small size and compact construction of the Dermatome, every desired graft site is completely accessible. The 35,000 cutting strokes per minute eliminates vibration and assures perfect control. Throw-away blades are easy to change.

Desired graft thickness is easily set by one simple lever — from 5/1000″ to 30/1000″. Maximum graft width is 3″. Stationary parts contacted by blade are carboloy for long wear. Only two parts to clean.

Dermatome rolls, rather than slides, requiring no skin preparation. Stryker skin tape can be used if desired.

Stryker Rolo-Dermatome guaranteed for two years.

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Color-Guide Drill Holder and Shield $28.00
Rhinoplasty Saw-Seltzer $132.00
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Automatic Screwdriver $24.50
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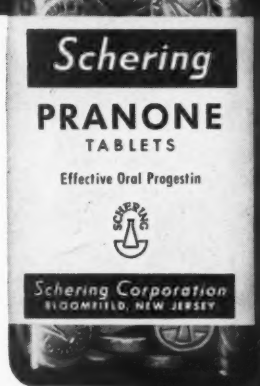
prevent periodic absenteeism . . .

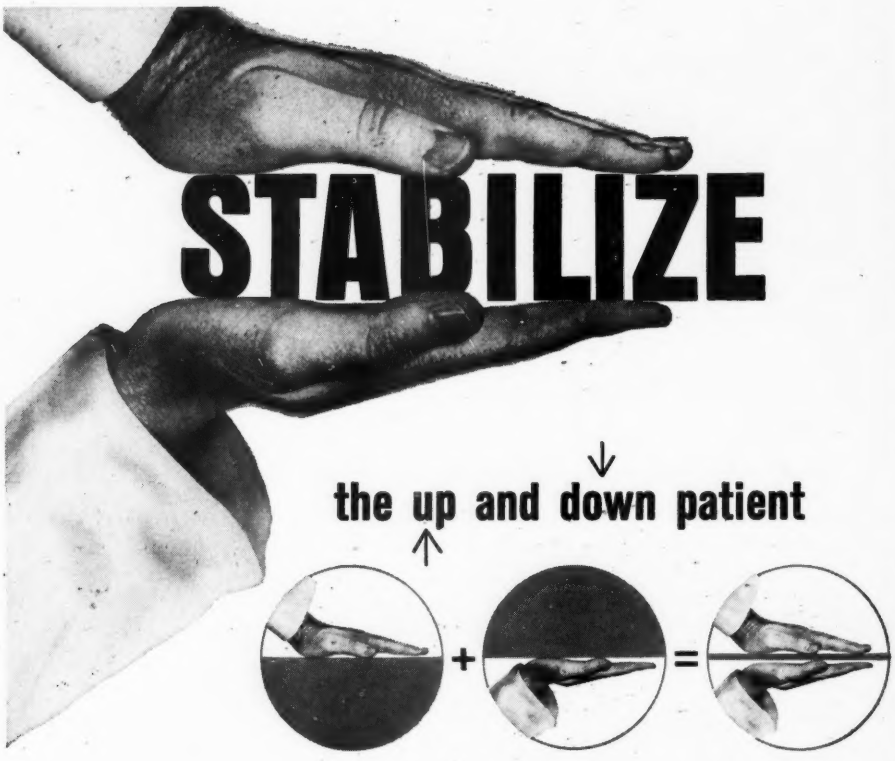
A major cause of absenteeism, dysmenorrhea represents a serious economic handicap to the more than one in three menstruating women with this complaint. PRANONE produces "brilliant results," and more physiologic relief of dysmenorrhea,* significantly reducing absenteeism from this cause.

PRANONE® Tablets (brand of Ethisterone U.S.P.) are available in 5, 10 and 25 mg. strengths.

* Parsons, L., and Tenny, B., Jr.: M. Clin. North America *34*:1537, 1950.

CL-J-51





To induce emotional equilibrium in those who swing from anxiety to depression, Serpatilin combines the relaxing, tranquilizing action of Serpasil with the mild mood-lifting effect of the new cortical stimulant, Ritalin. In recent months, numerous clinical studies have indicated the value of combining these agents for the treatment of various disorders marked by tension, nervousness, anxiety, apathy, irritability and depression. Arnoff,[1] in a study of 51 patients, found the combination of definite value in a variety of complaints, noting no effect on blood pressure or heart rate. Lazarte and Petersen[2] also found Serpatilin effective in counteracting the side effects of reserpine and chlorpromazine. They reported: "The stimulating effect of Ritalin seemed complementary to the action of reserpine . . . in that it brought forth a better quality of increased psychomotor activity."

1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

Serpatilin Tablets, 0.1 mg./10 mg., each containing 0.1 mg. Serpasil® (reserpine CIBA) and 10 mg. Ritalin® hydrochloride (methyl-phenidylacetate hydrochloride CIBA).

Dosage: 1 tablet b.i.d. or t.i.d., adjusted to the individual.

CIBA
SUMMIT, N. J.

Serpatilin T.M.

(reserpine and methyl-phenidylacetate hydrochloride CIBA)

2/2289M

LEVOPHED® "...benefited these patients more than other pressor drugs..."[1]

in surgical

shock

LEVOPHED (levarterenol) given promptly raises blood pressure in seconds in surgery, hemorrhage, trauma, anesthesia.

Among 111 patients, "...99 exhibited an appreciable increase in blood pressure ...Many had shown no response to blood transfusions alone." In another series of 75 patients in profound circulatory collapse Levophed was found most useful where the shock was due to spinal anesthesia, sympathectomy or hemorrhage during surgery. In this "most useful" group the survival rate was 94 per cent as compared to 40 per cent in the total series.[1]

With LEVOPHED – onset of action almost immediate... pressor effect easily, accurately controlled... peripheral vasoconstriction only...blood pressure levels maintained almost indefinitely...heart rate slowed, coronary arteries dilated, oxygen supply to heart increased...shock damage to kidney and brain prevented.[1]

LEVOPHED bitartrate

natural antishock pressor hormone

1. Eckenhoff, J. E.; and Dripps, R. D.: Anesthesiology, 15:681, Nov., 1954. 2. Sokoloff, Louis; King, B. D.; and Wechsler, R. L.: Med. Clin. North America, 38:499, Mar., 1954.

LEVOPHED (LEVARTERENOL), TRADEMARK REG. U. S. PAT. OFF.

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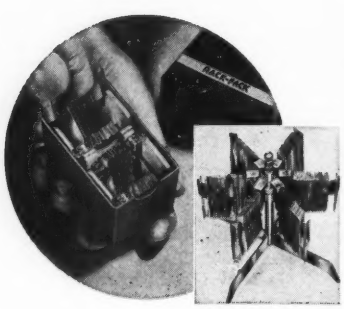

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SURGICAL OPERATING TABLE

The unexcelled versatility of the American ten-eighty surgical operating table is measurably increased by new and specialized accessories which facilitate the complete range of modern operative procedures.

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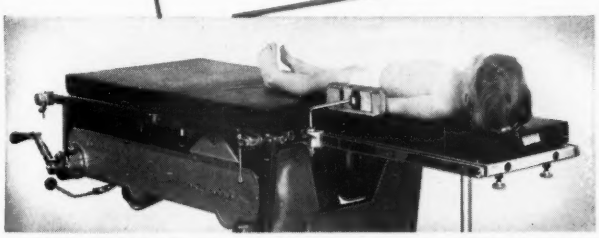
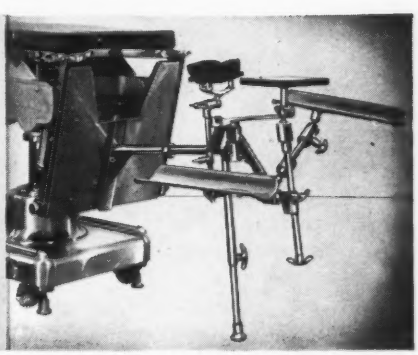
Your copy of Accessory Brochure C-183 is available upon request.



Narrow Table Attachment for infant surgery and head and neck surgery permits surgeon ideal proximity to operative site.

Illustrating use of Arm Support, Headrest and Restraint Strap appropriate for a neurosurgical procedure in the upright position.



Thoracic Frame for prone positioning provides unobstructed access to the operative site, minimum shock to patient and progressive posturing during procedure.

Now, for only $4950* G. E. brings you complete 200-ma x-ray facilities

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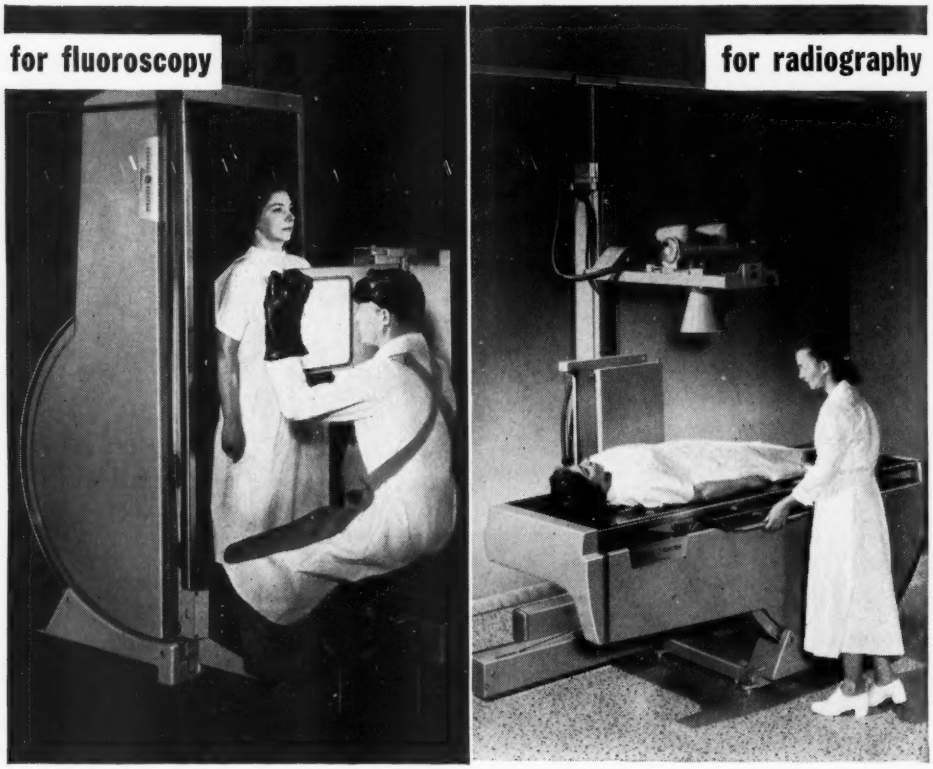

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MAJOR ADVANTAGES: Rapidly traverses the second stage, rarely nauseating, does not affect circulatory system or depress respiration.[1]

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(VINYL ETHER FOR ANESTHESIA U.S.P., MERCK)

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OTHER INDICATIONS: For short operative procedures and as a supplement to nitrous oxide or ethylene.

SUPPLIED: In boxes of three 10-cc. bottles and in bottles of 25, 50, and 75 cc., each with adjustable plastic dropper cap.

Reference: 1. Adriani, J.: *Techniques and Procedures of Anesthesia*, Charles C Thomas, Springfield, Illinois, 1952, pp. 92-95.

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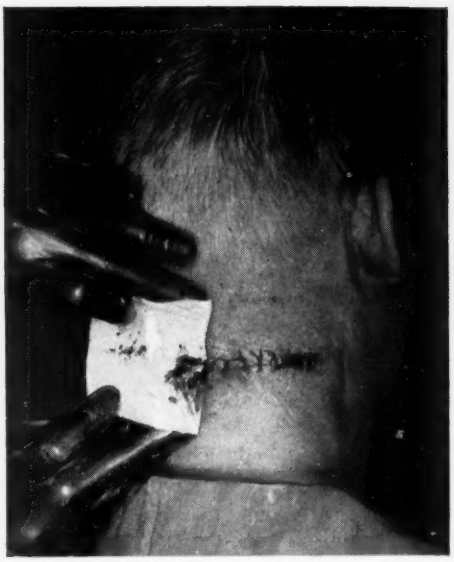
TELFA lifts off easily without sticking, even from this very long midline incision. Stitches are never irritated nor is healing disturbed.



Note easy removal of TELFA on 6th day after excision of neck tumor. Wound is dry, healing is well-advanced, and removal is painless.

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with muscle-relaxing action
...relieves tension

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1. the outer layer of antacids comes in contact with the gastric mucosa first . . . and after it is completely dissolved . . .

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A. positive antacid action to minimize gastric distress.

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References: 1. Boland, E. W., *J.A.M.A.* **160**:613, February 25, 1956. 2. Margolis, H. M., *et al. J.A.M.A.* **158**:454, June 11, 1955. 3. Bollet, A. J., *et al. J.A.M.A.* **158**:459, June 11, 1955.

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2.5 mg.

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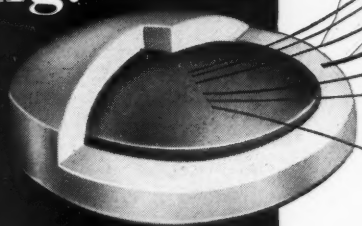

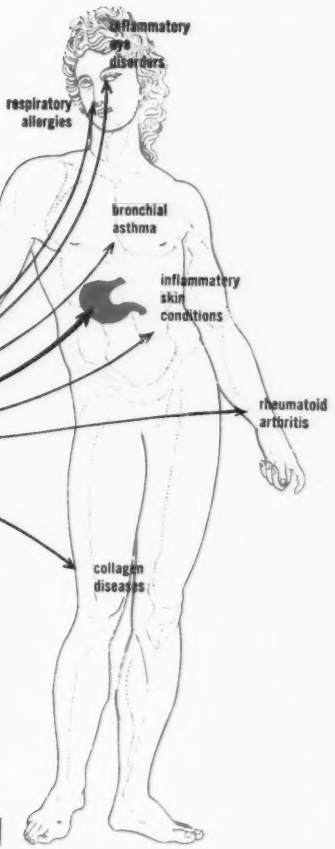

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1. Moyer, J. H., in discussion of Galen, W. P., and Duke, J. E.: Outpatient Treatment of Hypertension with Hexamethonium and Hydralazine, South. M. J. *47*:858 (Sept.) 1954.

2. Finnerty, F. A., Jr.: The Value of Rauwolfia Serpentina in the Hypertensive Patient, Am. J. Med. *17*:629 (Nov.) 1954.

3. Cronheim, G., and Toekes, I. M.: Comparison of Sedative Properties of Single Alkaloids of Rauwolfia and Their Mixtures, Meet. Am. Soc. Pharmacol. & Exper. Therap., Iowa City, Iowa, Sept. 5, 1955.

4. Moyer, J. H.; Dennis, E., and Ford, R.: Drug Therapy (Rauwolfia) of Hypertension. II. A Comparative Study of Different Extracts of Rauwolfia When Each Is Used Alone (Orally) for Therapy of Ambulatory Patients with Hypertension, A.M.A. Arch. Int. Med. *96*:530 (Oct.) 1955.

The dose-response curve of Rauwiloid is flat, and its dosage is uncomplicated and easy to prescribe...merely two 2 mg. tablets at bedtime.

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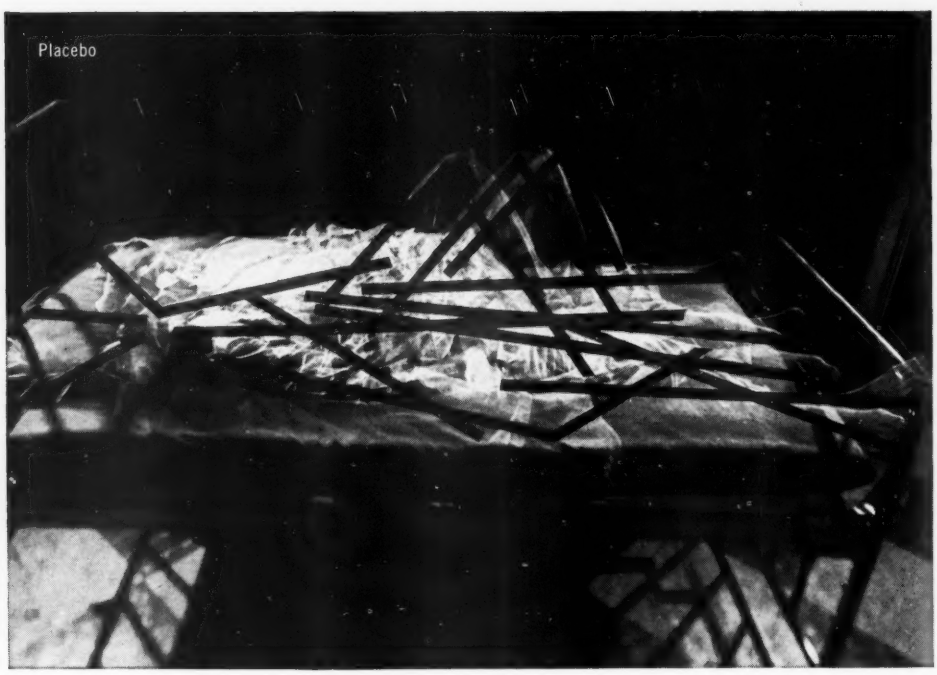

Twenty-eight-year-old male, restless sleeper, tense personality with occasional insomnia, was photographed at fixed intervals during the night to produce a series of exposures on same sheet of film. On placebo (above), unique "stroboscopic" picture shows him in typical fitful night of unrest.

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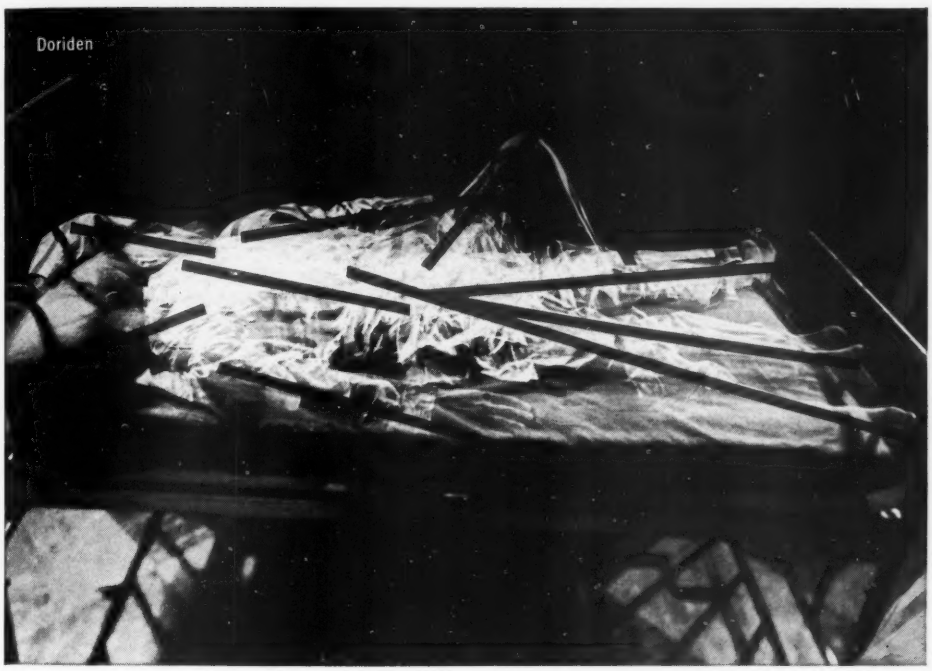

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TABLETS, 0.125 Gm., 0.25 Gm. (scored) and 0.5 Gm. (scored).

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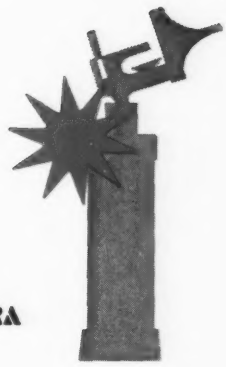

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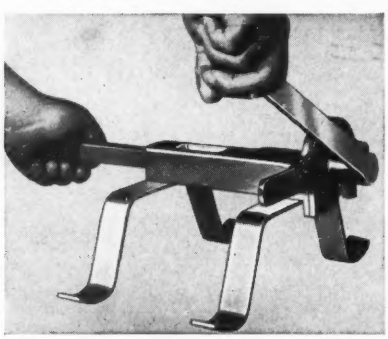

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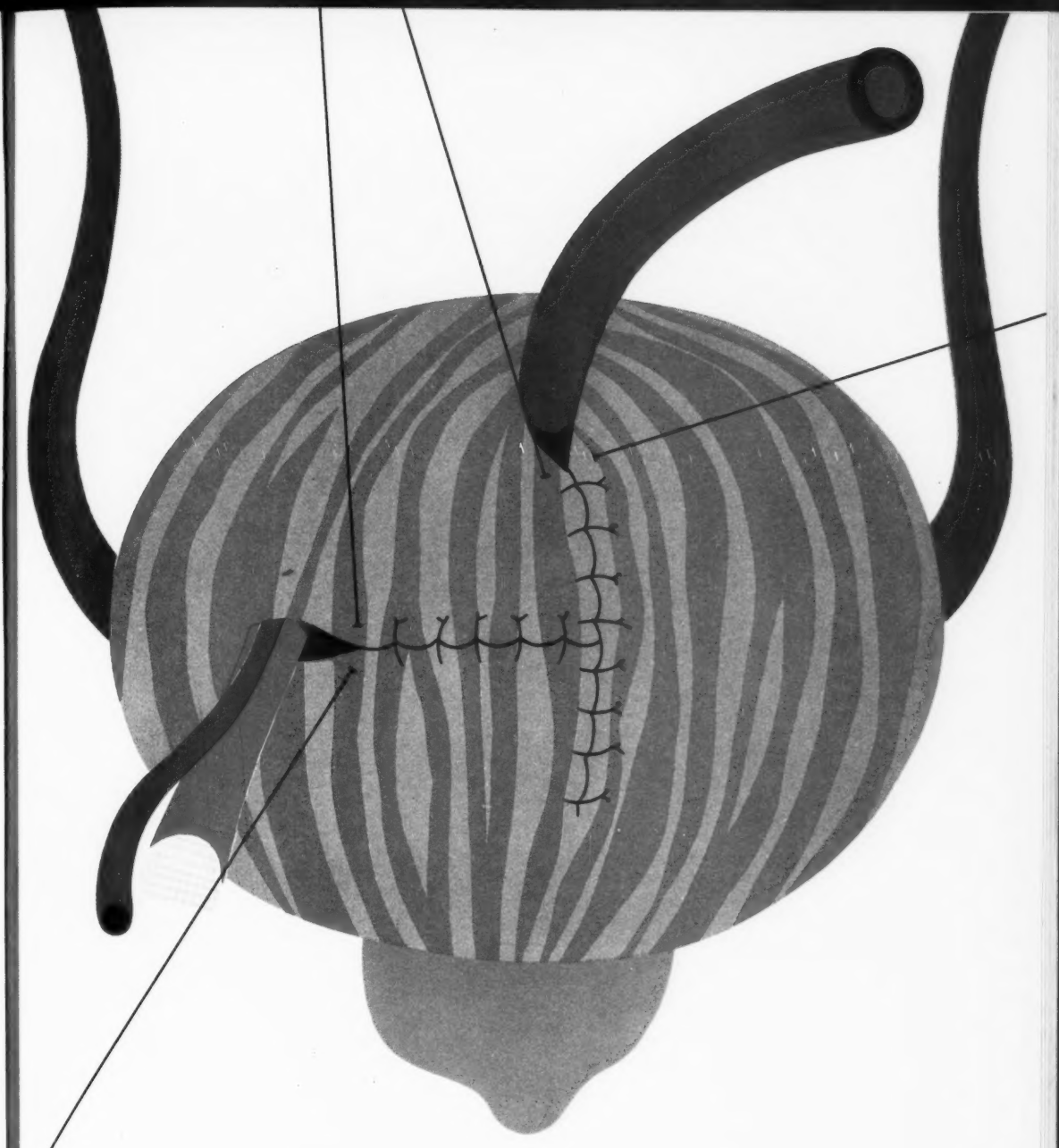

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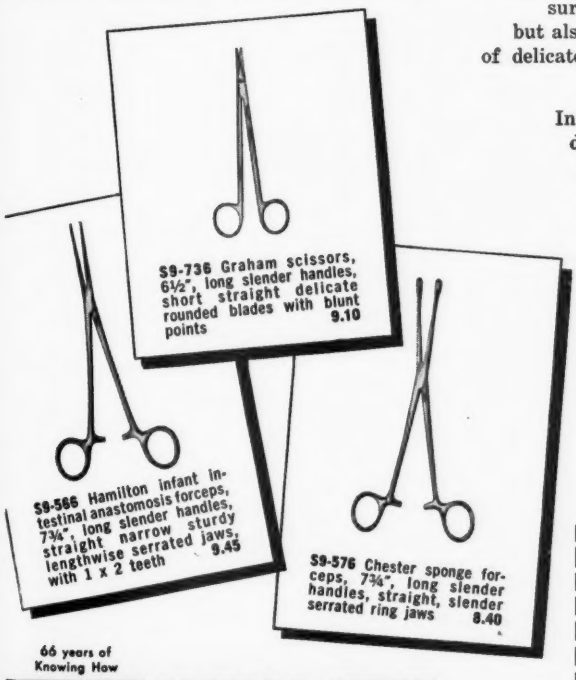

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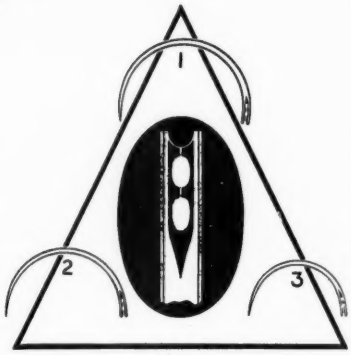

Fig. 6

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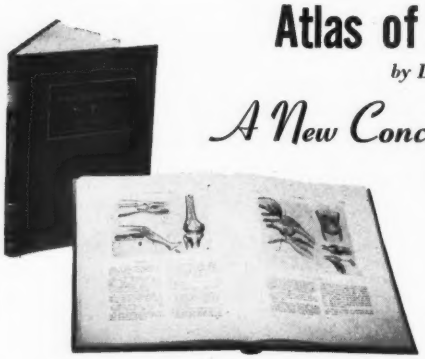

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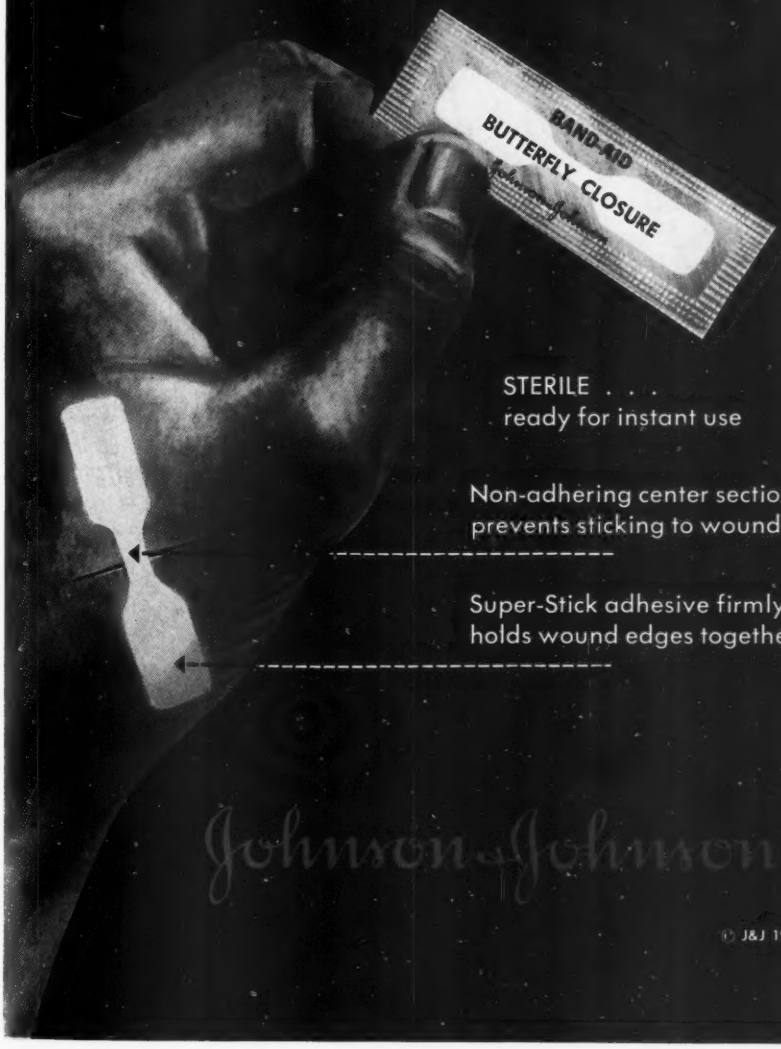

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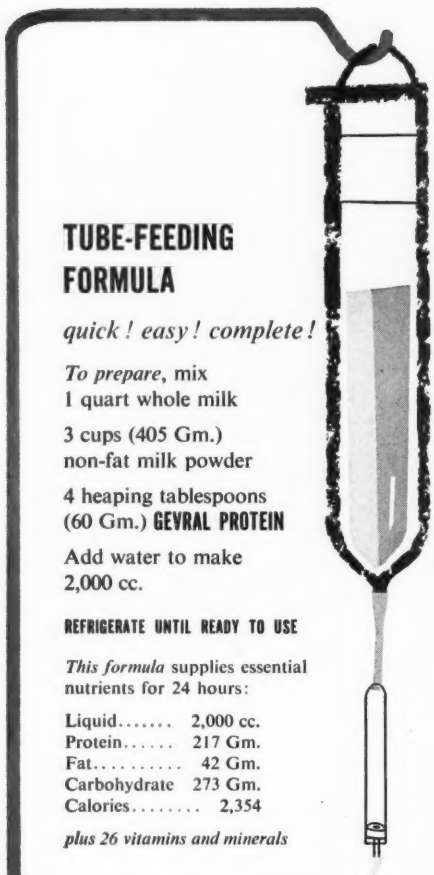

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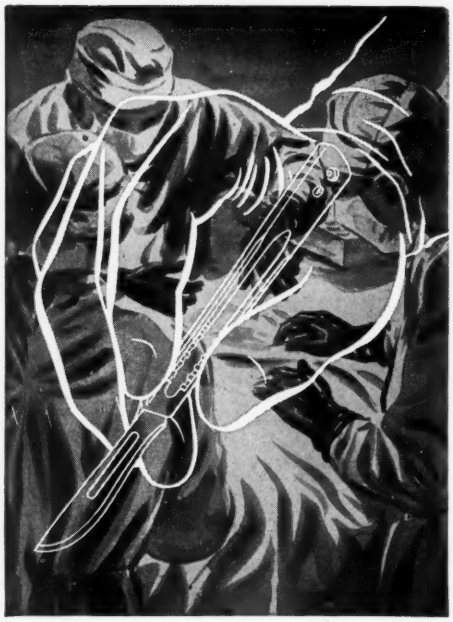

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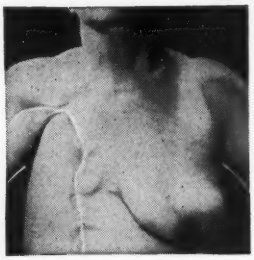

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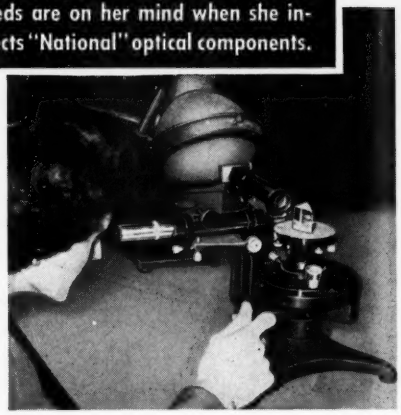

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References: 1. Rhoads, J.E.: Internat. Abstr. Surg. *94*:417, 1952. 2. Mecray, P., Jr.: Am. J. Clin. Nutrition *3*:461, 1955. 3. Cannon, P.R.: J.A.M.A. *135*:1043, 1947. 4. Halpern, S.L., in Nutrition in Infections, Miner, R.W., ed.: Ann. New York Acad. Sc. *63*:147, 1955.

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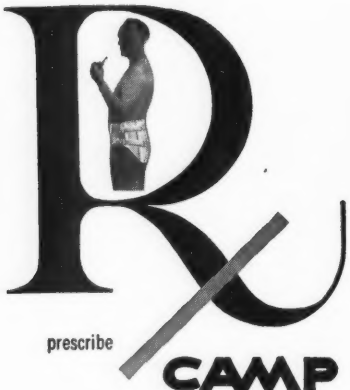

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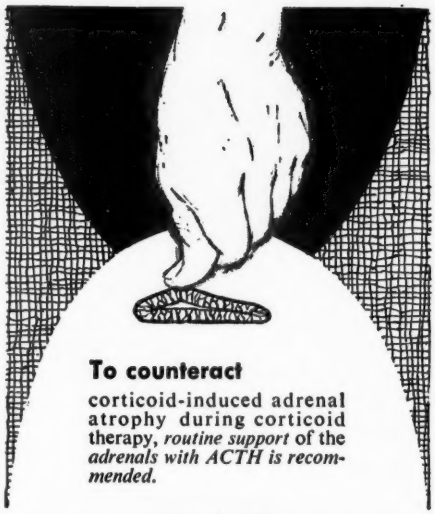

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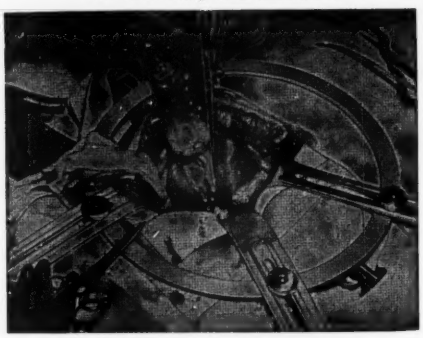

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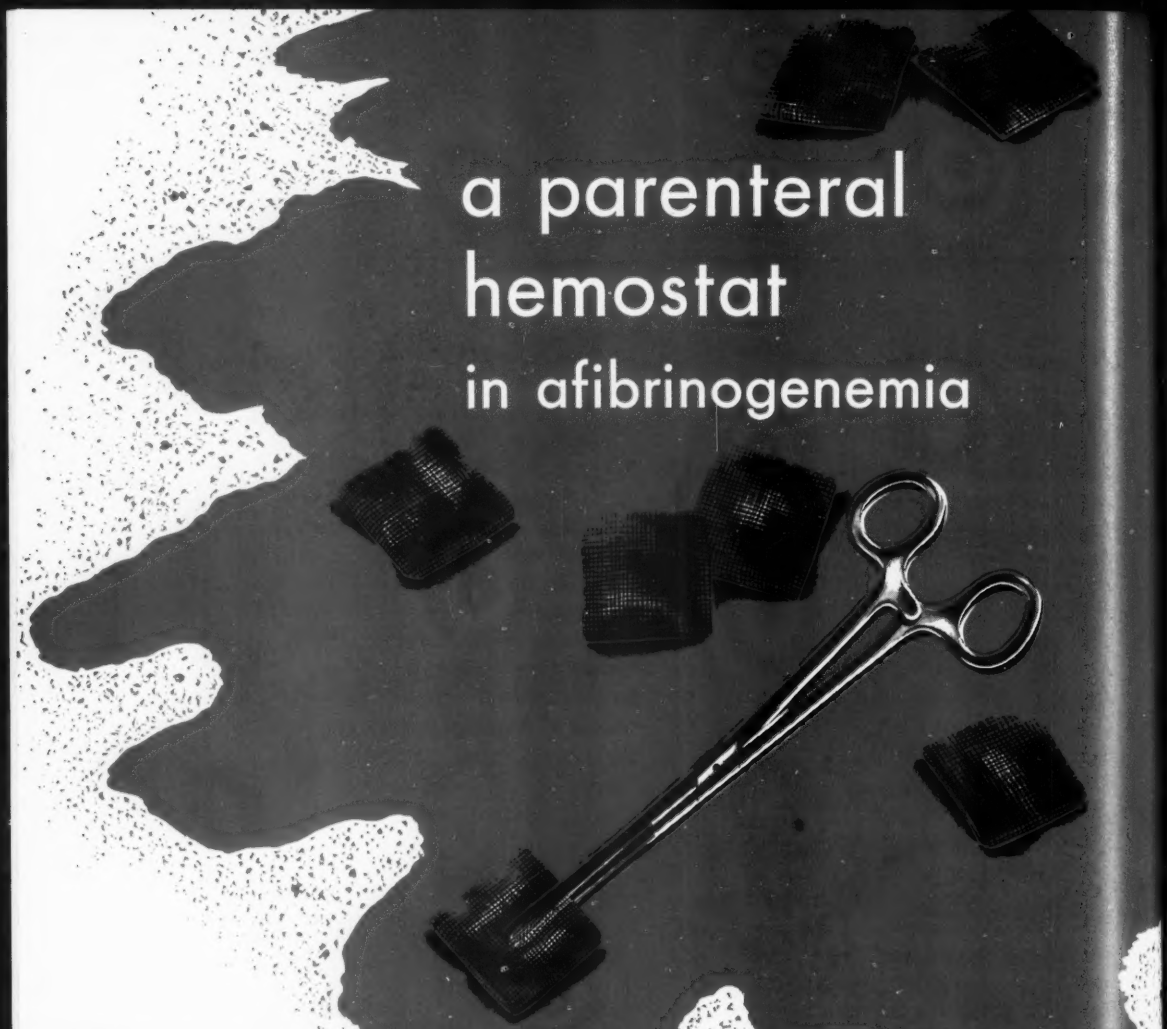

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1. Bonica, J. J.: *Anesthesiology*, 11:716, Nov., 1950.
2. Moore, D. C.: *J. A. M. A.*, 146:803, June 30, 1951.
3. Bonica, J. J.: *Anesth. & Analg.*, 30:76, Mar.-Apr., 1951.
4. Bonica, J.J.: The Management of Pain. Philadelphia, Lea & Febiger, Sept., 1953.
5. Moore, D.C.: Regional Block. Springfield, Ill., Charles C. Thomas, 1953.

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1. Mathews et al.: Am. Pract. & Dig. Treat. 6:560 (Mar.) 1955.
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